THE UNIVERSITY OF LIVERPOOL

The Identification and Evaluation of Suspected Adverse Drug Reactions in Neonates

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Abstract

Adverse drug reactions (ADRs) in neonates exhibit different profiles to those seen in older children and adults. Neonates are a unique population who exhibit their own risk factors for developing ADRs, one of which is the high proportion of off-label drug use. However, a lack of appropriate methods for the detection and assessment of ADRs in this population means the rate of underreporting is high, and thus little influence on improving medicines for neonates can be expected from pharmacovigilance. The aim of this research was to generate prospective neonatal ADR data to allow the comparison of several causality assessment tools in the neonatal setting. A prospective observational study conducted at the Liverpool Women's Hospital neonatal unit collected suspected cases of neonatal ADRs. A sample of these cases were analysed by six different assessors using three existing causality assessment tools; the Karch and Lasagna algorithm, the 'New Adverse Drug Reactions Algorithm for Infants in the Neonatal Intensive Care Unit' algorithm (Du Lehr), and the Liverpool ADR Causality Assessment Tool (LCAT). Statistical analyses were performed to evaluate the inter-rater and inter-tool reliability when using the three methods. Over a period of nine weeks, 63 cases of suspected neonatal ADR cases were collected, detailing a wide range of ADRs to many different drugs, almost 50% of which were prescribed off-label. When a sample of 34 of these cases were assessed for causality using the three methods, global kappa scores of less than 0.3 for each tool suggested only 'fair' inter-rater reliability was exhibited by each method. Inter-tool reliability measures suggested that the consistent use of one methodology within and across pharmacovigilance studies will produce more reliable results than varying methods. The results of this research suggest that the three tools evaluated may need to be adapted before they can be used to reliably assess neonatal ADRs.

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Publications and outputs

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Poster presentation:

Adverse drug reactions in neonates: Comparing retrospective spontaneous Yellow Card reports to prospectively collected reports

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List of abbreviations

ADR	Adverse Drug Reaction
ADRIN	Adverse Drug Reactions in Neonates
ADRIC	Adverse Drug Reactions in Children
AKI	Acute Kidney Injury
ANNP	Advanced Neonatal Nurse Practitioner
ATC	Anatomical Therapeutic Chemical (classification)
BP	Blood Pressure
BNFc	British National Formulary for children
CI	Confidence Interval
CYP	Cytochrome P450
EMA	European Medicines Agency
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HCA	Healthcare Assistant
HDU	High Dependency Unit
HRA	Health Research Authority
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRAS	Integrated Research Application System
ITU	Intensive Treatment Unit
IV	Intravenous
LCAT	Liverpool ADR Causality Assessment Tool
LWH	Liverpool Women's Hospital
MHRA	Medicine and Healthcare products Regulatory Agency
NICU	Neonatal Intensive Care Unit
PDA	Patent Ductus Arteriosus
PICU	Paediatric Intensive Care Unit
REC	Research Ethics Committee
SHO	Senior House Officer

TPN	Total Parenteral Nutrition
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Background

Approximately 90,000 neonates are admitted to neonatal units each year in the UK(1,2). Many of these neonates will be prescribed medicines, and yet most previous pharmacovigilance studies have omitted all or part of the inpatient neonatal population from their work. An adverse drug reaction (ADR) is defined by the World Health Organisation as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man'(3). Recent studies into adverse drug reactions in children have indicated a considerable health risk for this population, with incidence rates ranging from 0.4% to 10.3% for paediatric hospital admissions related to ADRs and 0.6% to 16.8% for the proportion of children experiencing an ADR during an admission(4). Between 2000 and 2009 the highest number of spontaneous ADR reports for children was for those under one year of age but to date there is limited research studying ADRs in neonates alone(5). A review of the UK 'Yellow Card Scheme' for spontaneous reports of ADRs found that only 97 reports of ADRs in neonates had been submitted in the 10 year period between 2001 and 2010(6). If an estimated 900,000 neonates were admitted to neonatal units during this time, there was approximately one report for every 9278 neonates admitted. Even if the lowest estimate of the incidence of ADRs in children is the most accurate, 3600 ADRs would have occurred in these 900,000 neonates. As only 97 reports were filed to the Medicines and Healthcare products Regulatory Agency (MHRA) this reflects an underreporting rate of 97%, which is in keeping with findings from other pharmacovigilance studies(6,7).

1.1.1 Definitions

Several definitions of an ADR are used currently. To monitor adverse drug reactions efficiently and effectively, it is important to harmonise the terminology used to describe ADRs. The World Health Organisation's definition of an ADR has been used for over 40 years(3). This definition has been criticised in the past for lack of clarity about the inclusion of minor side-effects. Further definitions more clearly exclude such effects, for example Laurence's definition, 'a harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration'(8).

In their review of such definitions, Edwards and Aronson concluded their definition as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'(9).

As with any surveillance, ADR monitoring, and thus the definitions used, should be population-specific. Allegaert et al suggested a definition more suitable for neonates as 'an unintended and harmful effect resulting from the use of medications intended for diagnostic or therapeutic reasons (irrespective of the dose)'(10).

Another issue is that the term 'neonate' refers to different populations in different work. The definition suggested from the International Conference on Harmonisation is a baby within 28 days of birth(11). However, this definition does not allow for the predating of prematurity and thus more advanced definitions include commentary on the use of estimated date of delivery for a more accurate measurement of age. A more appropriate definition is up to 44 weeks post menstrual age, where post menstrual age is time from first day of last normal menstrual period to day of assessment. This definition has been adopted by the European Medicines Agency as outlined in the guideline on the investigation of medicinal products in the term and preterm neonate(12).

It is quite possible that the lack of a clear definition of an ADR is contributing to underreporting. The absence of a universally accepted definition combined with recent changes in Medicines and Healthcare products Regulatory Agency (MHRA) guidance regarding ADR reporting leaves individuals confused about when and what to report, such that the easier option is to not report at all(13).

1.1.2 ADRs as an important health problem

The importance of ADRs in relation to hospital mortality was highlighted in a systematic review suggesting they could be the 4th largest cause of death in the USA(14). The incidence of adverse drug reactions that cause admission to hospital is estimated to be 4-7% in the adult population(15,16). One of the largest research programmes about ADRs in children to date was conducted at Alder Hey Children's Hospital in Liverpool (ADRIC: Adverse Drug Reactions in Children). In this study, 17.7% of inpatient children experienced at least one ADR(17). Of the admissions 2.9% were related to an adverse drug reaction(18). Only limited data about neonatal admissions related to ADRs exists. Although one of the largest studies of its kind, ADRIC only included surgical neonatal care data, at the request of the funder's peer review. There is therefore a need to include tertiary neonatal medical care in future pharmacovigilance research. The Adverse Drug Reactions in Neonates (ADRIN) project is an extension to the ADRIC study that considers neonates. This study is the first element of ADRIN and focuses on methodological issues.

As well as being an important problem for the health of a population, ADRs contribute to healthcare expenditure. A study set in two Merseyside hospitals, Royal Liverpool University Hospital and Wirral Hospitals NHS Trust, found that 6.5% of admissions among adults related

to an ADR, of which 80% were directly due to the ADR. These admissions accounted for 4% of the hospitals' bed capacity. When extrapolated to the whole NHS, the cost of ADRs was estimated to be £466m (2004; €706m, $847m)(15). In an international multicentre study of 328 identified ADRs in a paediatric population, hospitalisation was increased by an average of two days among those children experiencing an ADR compared to those who did not(19).

1.1.3 Medicines use in neonates

The clinical speciality of neonatology usually revolves around the care of neonates who are born prematurely, who incur illness as a result of labour or delivery, or who have developed illness in utero. Sick neonates are often hospitalised for weeks or months after birth and can be exposed to multiple medications throughout their time as an inpatient. As with any sub-specialty of medicine, some medicines are commonly prescribed. The complex and unusual illnesses presenting to a neonatal unit, often require a wide range of medicines.

A linear correlation between the incidence of ADRs and exposure to an increasing number of medications has been demonstrated(20). One study conducted in a neonatal intensive care unit reported that 29.6% of neonates received more than four medications and 7.6% received 10 or more(21). Further studies show that up to 90% of inpatient neonates in intensive care receive off-label or unlicensed medications, which multiple studies suggest is a risk factor for developing an ADR(22-24). There are also some medications which have specific harms in neonates (table 1, (11)). Despite emerging data regarding medicines that can be harmful to neonates, some of these medicines with published safety warnings are still used in NICUs worldwide e.g. meropenem, itraconazole and sulfadiazine, suggesting that the risks need to be considered in parallel with the benefits(24).

Table 1 Drugs known to cause ADRs that are specific to neonates

Drug	Recognised neonatal ADR
Ceftriaxone and calcium co-administration	Death due to precipitation of ceftriaxone-calcium salts
Chloral hydrate	Encephalopathy
Chloramphenicol	Grey-baby syndrome due to reduced glucuronidation in this age group compared to other ages
Codeine	Respiratory depression exacerbated by genetic polymorphisms
Corticosteroids	Restricted growth, altered brain development, hyperglycaemia
Kaletra (lopinavir/ritonavir)	Adrenal dysfunction in HIV-infected infants
Indomethacin	Oliguria
Oxygen	Retinopathy of prematurity at high doses
Sulphonamides	Kernicterus due to displacement of bilirubin from plasma proteins
Tolazoline	Oliguria
Vitamin E	Sepsis
Propylene glycol (as an excipient)	Hyperosmolarity, lactic acidosis and renal/hepatic toxicity

In addition to the associated harms, neonates have unique opportunities to benefit from medicines. For example, caffeine is a drug used frequently in neonatal care to treat apnoea of prematurity, but it was also found to increase the rate of survival without neurodevelopmental disability in children at 18-21 months corrected gestational age(25).

A recent quasi-systematic review was conducted into medicines use in neonatal intensive care units (NICUs) across 12 different countries, including the UK, Ireland and the USA(24). Gentamicin and ampicillin were the most commonly cited medicines used, followed by caffeine, furosemide and multivitamins. Four other antibiotics were in the top 20 most commonly cited medications along with surfactant, dopamine and morphine. The differences in medications prescribed between countries was deemed insignificant and the median number of medicines prescribed per neonate ranged from three to eleven(24). However, a pan-European study found significant differences in the use of antibiotics across 21 countries. Differences were apparent in the proportion of neonates receiving systemic antibiotics and the dosing of the most frequently used antibiotics(26). In relation to patterns of medications prescribed, not all studies included in the quasi-systematic review reported on the same influencing factors. Three main observations were drawn from what was described; the number of medications prescribed is inversely proportional to gestational age and weight, and mortality rate is inversely proportional to gestational age. In agreement with previous research the review found 71%-100% of neonates were prescribed unlicensed or off-label medications, more often in preterm than term neonates(24).

A paper outlined the changes in drug utilisation on a NICU between 1997 and 2004(27). The analysis revealed significant changes in the drugs used over time on this single NICU, including an increased use of antibiotics, cardiovascular, endocrine, gastrointestinal and central nervous system drugs. The ophthalmic drugs group was seen to decrease in use. It is likely that the increased number of neonates who are surviving preterm birth, and the improving detection of congenital abnormalities in utero, is contributing to these changes(27). However, the patterns of change across multiple sites worldwide would need to be analysed to better explore this.

1.1.4 Medicines research in neonates

Historically, medicines research in neonates and young children has been infrequent, with many pharmaceutical companies deciding not to include a paediatric population in their trials due to difficulty overcoming perceived ethical issues, and the lack of incentive for the extra cost and time. Nevertheless, some of the worst tragedies in the pharmaceutical industry involved neonates and prompted medicines legislation to encourage and improve medicines research for neonates and children.

Thalidomide is probably the most widely known of these tragedies. In the late 1950s and early 1960s, thalidomide was prescribed to pregnant women across Europe, Japan and Australia for the treatment of morning sickness. By 1961, the drug had been banned in most countries after approximately 10,000 children were born with limb reduction abnormalities. Further defects, including heart, eye and ear abnormalities were also ascribed to thalidomide use. Laboratory studies had not produced the same effects in mice. Resulting from this tragedy, drugs now require systematic developmental toxicity testing in at least two separate species before authorisation for market. Thalidomide is used today to treat multiple myeloma and leprosy(28).

Lesser known tragic ADRs include Gray baby syndrome; severe cyanosis, abdominal distension and cardiovascular collapse in neonates following treatment with chloramphenicol. Reye's syndrome, which was linked to the use of aspirin in children, is now virtually eliminated as a result of reports to the Yellow Card Scheme. There was a period of 81 years, however, between first introduction of aspirin into clinical practice and the identification of a causative link between its use and Reye's syndrome(29, 30) .

The drive to produce better medicines for children has recently included work on designing age-appropriate formulations. For example, the practice of crushing a tablet and mixing half the powder into food or drink presumes equal distribution of the active ingredient within the tablet, as well as increasing the risk of losing active ingredient. There has been limited research about the management of age-inappropriate formulations, for example through manipulations, despite the widespread use of manipulations. A systematic review of dosage form manipulation identified a lack of evidence to support this practice in paediatrics. Of the 50 studies that were included in the review, only two included paediatric settings and the majority of studies detailed tablet manipulations in adults(31). An observational study of drug manipulations occurring in three paediatric inpatient settings identified 310 manipulations when reviewing the 18 included wards for two weeks each. The highest number of observed manipulations occurred in neonatal settings and 68.2% of IV drug manipulations occurred on the neonatal wards(32). The need to manipulate medicines for children could also be contributing to inappropriate dosing causing adverse effects. Designing medicines for children that do not need to be manipulated to allow accurate dosing should be encouraged.

Legislation

Over the past few decades the expectation that children should be given medicines suitable for their bodies and needs has grown. Without further paediatric medicine development, clinicians are too often left with no choice but to prescribe unlicensed or off-label medicines to this most vulnerable population.

In recent years, regulations have been put in place to attract pharmaceutical companies to produce medicines for children, as is the case in the EU and the USA(33). However, regulations are only beneficial if they encourage change and improvement. The impact of the EU and US regulations is still being examined since they are relatively new, but there is evidence to suggest a positive influence. The 'Physician's Desk Reference', used by US clinicians for prescribing guidance, has seen a 21% increase in the number of new medical entities with paediatric information when comparing 1999 to 2002-2008(34). Over 90% of the 500 labelling changes approved by the US Food and Drug Administration (FDA) federal agency between July 1998 and September 2011 resulted from paediatric studies requested under the new regulations. Following the implementation of EU regulations and before the end of 2011, 24 Paediatric Investigation Plans (PIPs) led to new paediatrics indications, and 77 to new paediatric formulations whilst a further five found medicines inappropriate for use in children(35).

Whilst EU and US regulations have promoted an improvement in paediatric drug research, neonates are still not receiving the same benefits as older children and adults, even though there is now widespread understanding that they exhibit different pharmacokinetics and pharmacodynamics. Following EU regulation until the end of 2011, only 60 of the 395 PIPs that were submitted for the opinion of the Paediatric Committee (PDCO) in the European Medicines Agency (EMA) included studies in neonates, whilst the remaining 335 sought waivers. The PDCO added neonatal inclusion to a further 50 of these remaining PIPs, suggesting some companies are not doing enough to attempt to design studies including neonates(35). Further studies are needed in the neonatal population to bring their safety of medicines in line with that of older children and the paediatric population in general.

Pharmacovigilance is a prominent part of the regulatory regime in Europe. Pharmaceutical companies must file a Risk Management Plan when a market authorisation is granted. This ongoing gathering of information about the risk-benefit assessment after authorisation will become increasingly important particularly with the rise of adaptive licensing, that is the staged approval of medicines(36). In Europe, the Pharmacovigilance Regulation is another important development(37). There is a growing need for methods to assess ADRs in neonates and it is important to characterise these methods.

Neonatal drug trials

Designing clinical trials in neonates faces many challenges for example, the lack of knowledge surrounding neonatal pharmacology (drug disposition and pharmacodynamic endpoints), particularly that relating to premature neonates. Should these barriers be overcome, there

remains the difficulty of using neonatal subjects for interventional research e.g. low blood volumes for sampling, difficulty measuring drug concentrations etc(38).

Recent studies, that have overcome the difficulties in designing a neonatal drug trial, have demonstrated the necessity of independent neonatal drug research. Anti-infectives provide some examples. Micafungin, an antifungal drug used for candidiasis infections, was demonstrated to have much higher total drug clearances in neonates than in older children and adults, suggesting a higher mg/kg dose is required in neonates(38). Several trials have also been conducted into the use of antibiotics in neonates, namely metronidazole, clindamycin, daptomycin, tazocin and meropenem. These studies reported the efficacy, safety and the pharmacokinetics of these drugs and how they differ from that known for older children and adults. Additionally, these studies show it is important to consider not only a difference in pharmacology between neonates and older children or adults, but also a difference between preterm and term neonates, and the effects of post-natal age, post-menstrual age and weight. These studies, like the limited amount of others of their kind, highlight that it is not valid to simply predict pharmacokinetics and pharmacodynamics of a drug based on its properties in older children or adults(38).

1.2 Neonatal pharmacology

Changes in the human body that occur as a child develops affect how the body handles the drug (pharmacokinetics) and responds to a drug (pharmacodynamics). Similarly, a drug has the potential to affect the body differently depending on the developmental stage of the body at which the drug is introduced. Development from birth to adulthood is a continuous process unique to each individual. As a result, it is difficult to categorise children into age groups or developmental stages that can be used to advise prescribing. Whilst a person over 18 years of age is generally accepted as an adult, it is almost impossible to definitively say when a neonate becomes an infant or an infant becomes a child. Prematurity complicates the transition from neonate to infant further.

1.2.1 Absorption

There are several age-related differences which affect the absorption of a drug in a neonate. Neonates have a larger gastrointestinal surface area relative to their size than adults, so have a relatively greater area for drug absorption. The neonatal gastrointestinal lining and skin are also more permeable at this age meaning drugs that may not be absorbed in a mature body could be absorbed in neonates and have the potential to cause harm(39,40). The surface area of the skin is similarly larger relative to their size, meaning care should be taken with the prescription of topical medicines such as steroid creams. The stratum corneum of neonatal

skin is thinner and the skin has a greater blood supply due to an immature vasomotor control. The premature neonate exhibits these features even more so(38).

1.2.2 Distribution

Protein-binding can dictate the distribution and elimination of a drug, but protein synthesis and binding varies with age and maturation. The combination of decreased concentrations of circulating proteins, namely albumin and α_1-acid glycoprotein, and a reduced affinity for drug-protein binding increases the concentrations of circulating drugs. Protein binding is thought to increase with age such that the problem of decreased drug-protein binding is even more profound in premature neonates. In the typical sick premature neonate, there is also potential for drug competition for protein binding if multiple drugs are prescribed. An acidotic state is also thought to affect protein binding(40).

1.2.3 Metabolism

The majority of drug metabolism in the liver is dependent on cytochrome P450 (CYP) enzymes. The type and quantity of CYP enzymes produced varies with time and age (40). In addition, the expression and activity of CYP enzymes, which are involved in the metabolism of many drugs, have been found to be affected by exogenous substances such as drugs and food in adults(41). Blake et al found that neonates who were fed formula feeds had an accelerated maturation of the metabolism of certain drugs due to the increased activity of CYP enzymes(42).

1.2.4 Excretion

Age-related differences in glomerular filtration rate (GFR), renal tubular secretion and resorption all contribute to the ability of the kidneys to clear drugs from the blood, and hence renal clearance increases with age (gestational and postnatal) and weight. The effect of reduced renal clearance is even more pronounced in premature neonates. Healthy neonates usually experience adult GFR by one year of age. The kidneys are not fully developed until 34 weeks gestation and thus this rise in GFR is initially less steep in premature neonates. Sick neonates may be further compromised by reduced renal blood flow from PDAs (patent ductus arteriosus) or nephrotoxic drugs such as gentamicin(38).

1.3 ADRs in neonates

Due to the difficulties in designing and justifying neonatal medicines research, the practice of monitoring the side effects of medicines is paramount as a non-interventional way of improving the safety of medicines for this population.

Pharmacovigilance is defined by WHO as ‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related

problem'(43). Pharmacovigilance should be incorporated into the role of any healthcare worker, but the rate at which ADRs are currently reported reflects that this is not the case, suggesting that the integration of pharmacovigilance into routine clinical practice needs improvement.

ADRs can be unpredictable, and clinicians should always be vigilant for the side-effects of medicines. Detailed history taking, examination, investigation and consideration of risk factors and differential diagnoses are imperative as with any diagnosis. Further to this, reviewing published literature of ADRs, from case reports to Cochrane reviews, helps the clinician to identify any supportive evidence for their suspicions. The use of causality assessment tools may also be helpful. Some research has attempted to develop tools that are appropriate for use in paediatric settings, but to date few tools exist to specifically assess paediatric ADRs, let alone neonatal ADRs.

ADRs should be reported to appropriate pharmacovigilance regulatory agencies. This aims to bring about change and contribute to the drive for safe and effective medicines, as well as alerting manufacturers. Anyone can now report an ADR in the UK, including patients and parents, but regularly changing guidance over reporting could be a source of confusion contributing to the rate of underreporting that is currently suspected.

1.3.1 ADRs in neonates - incidence

The ADRIC research programme conducted in Alder Hey Children's Hospital between 2008 and 2009 found that 2.9% of admissions were due to ADRs(18). Among children who spent more than 48 hours in the same hospital, 18% experienced at least one ADR(17). Both studies only included a surgical neonatal setting. ADRs have been found to be responsible for 0.2% of neonatal admissions(44). Whilst inpatient stays generate the most medicine use, this admissions figure still represents 180 neonates a year in the UK. The incidence in paediatric outpatients has been estimated to be much lower(45). A recent prospective observational study into ADRs in neonates found an incidence of 17% when 313 neonates were studied in 13 months(46). The most recent estimate, published in April 2017, was higher at 27.4%(47). To provide an accurate estimation of ADR incidence, a large cohort of neonates needs to be studied over a considerable period.

1.3.2 ADRs in neonates - causative drugs

In the UK between 2001 and 2010, the swine flu vaccine and caffeine generated the most neonatal Yellow Card reports (8 and 5 respectively), with a total of 68 different medications being suspected to have caused a neonatal ADR. Despite approximately 7% of neonates receiving antibiotics to treat infection there was a reporting rate of one antibiotic Yellow Card report per year for neonates(6). Thousands of neonates born preterm and term receive

surfactant to aid lung function and reduce the need for mechanical ventilation. However, there were no Yellow Card reports of surfactant causing an ADR in a neonate between 2001 and 2010, despite the BNF listing several possible ADRs to surfactant. Though listed as rare, these include bradycardia, decreased oxygen saturation, hypotension and pulmonary haemorrhage(6,48). A search of the MHRA's interactive Drug Analysis Profiles shows there has only ever been 53 Yellow Card reports for surfactant, 29 filed for colfosceril (exosurf) and 24 under the general pulmonary surfactants category. Apart from two reports, these were all filed in the 1990s. The reports mainly detailed respiratory reactions and 15 reports detailed fatal outcomes(49). However, the Drug Analysis Profiles detail all Yellow Card reports but do not make commentary on whether the reactions detailed have been proven to be related to the drug or not. Belén Rivas et al reported in their recent prospective observational study that caffeine citrate, ibuprofen and ferroglycine sulphate generated the highest number of ADRs. Antibiotics as a collective group generated a high total percentage of all reported ADRs, and antibiotics and caffeine citrate were the drugs prescribed most frequently on the unit(46). Systemic anti-infectives were also the drugs most frequently suspected to have caused an ADR in a recent observational study in neonates in Columbia(47).

A recent review paper detailed several drugs which are uniquely harmful to neonates, exemplifying the danger of extrapolating understanding about the side-effects of drugs in adults or children(11). Verapamil is used to treat supraventricular tachycardia in adults, so was presumed safe for the same indication in neonates. Its use for this indication has been stopped since it was associated with a series of infant deaths(40).

It is not only the active ingredient in drugs which can cause an adverse drug reaction. An excipient is a substance that is contained within the drug to help with the stability, solubility or form of the drug itself yet still has pharmacodynamic potential. A recent study conducted in Estonia identified that 97% of 348 neonates included in the study received at least one excipient classified as being potentially harmful and 88% of the neonates received at least one of the excipients known to be harmful specifically to neonates(50). Of the medicines prescribed on the two units included in the study, 68% contained excipients classified as being potentially harmful(50).

This study however was conducted in one country only and prescribing practises may differ elsewhere. A pan-European observational study into the potentially harmful excipients in neonatal medicines included 21 countries. Of the 2095 prescriptions that were analysed, 31% contained at least one of the eight potentially harmful excipients that this study looked at, the most frequent of these being parabens. The prescriptions were administered to 63% of the neonates studied. The study also reported that geographical region determined the frequency

of prescription of four of the eight potentially harmful excipients, suggesting that alternative safer options are available and could be used to avoid side-effects(51). These studies identified that neonates are prescribed potentially harmful excipients but did not investigate whether any harmful adverse reactions occurred due to the prescriptions. Credible reports of suspected neonatal adverse drug reactions to excipients do exist elsewhere(52).

There are further sources of ADRs to be considered in neonates including those drugs administered to the parents of the neonate pre-conception, in pregnancy, in labour and during breast feeding.

Medication use in pregnancy

A recent multinational cross-sectional web-based study found that 81.2% of women reported using at least one medication in pregnancy(53). Reports suggest that exposure to medications from a maternal source causes a significant portion of ADRs in children under two(54). A recent retrospective review of Yellow Card reports between 2001 and 2010 reported that there were 248 reports of transplacental ADRs detailing 221 different medications. Fluoxetine was the most commonly reported medication and 16 different psychotropic medications produced just over 100 reported reactions(6).

Medication use whilst breastfeeding

In the same retrospective review of Yellow Card reports, fluoxetine was also the most commonly reported drug in cases of suspected transmammary ADRs(6). A recent literature review of neonatal and infant ADRs to drugs in breast milk identified case reports of reactions to 45 different medications, all of which were identified as being probable or possible adverse drug reactions using the Naranjo algorithm(55). As with all ADRs, the clinical signs and symptoms of the reaction may not be evident immediately. In this review some of the reactions, such as hyperactivity and speech delay, only became apparent when the child was over four years old(55).

Fathers using medication at time of conception

Medications prescribed to fathers preconception are also a source of adverse drug reactions in foetuses or neonates. Hawcutt's review of Yellow Card reports between 2001 and 2010 in the UK identified three reports detailing six reactions to four paternal drugs, all of which were reported by doctors. The four drugs reported were all used to treat autoimmune conditions and were suspected to have caused growth retardation, diarrhoea, developmental delay, hypotonia, fetal cardiac abnormality and development of a birth mark(6). However, a recent prospective observational multicentric study conducted in Italy followed the pregnancies and neonatal outcomes related to fathers with multiple sclerosis exposed and not exposed to

disease-modifying drugs at time of conception. The study found no significant association between fathers taking disease-modifying drugs and risk of spontaneous abortion or malformations. The length of time the children born in this study were followed up for varied from 0.1-10.7 years, thus little commentary can be made on the long term effects of paternal drugs taken around the time of conception(56). This is an area of pharmacovigilance that may offer more information with further investigation.

Maternal use of recreational and illicit drugs

Recreational and illegal drugs can also cause adverse drug reactions in the unborn child, some of which may not become apparent until the child is older. The effects of alcohol and tobacco are probably the most widely understood, and frequent media coverage and changing guidance means most women will aim to avoid both in pregnancy. Prenatal tobacco exposure has been shown to increase the risk of the child developing hearing difficulties, respiratory disease and metabolic disease. Alcohol consumption during pregnancy puts the unborn child at risk of Fetal Alcohol Spectrum Disorder which cannot be diagnosed until the effects can be assessed once the child is born. The spectrum includes a range of symptoms including pre and postnatal growth restriction, craniofacial abnormalities, hyperactivity and learning difficulties (57).

In the case of illicit drug use it may be difficult to determine fetal effect for several reasons; lack of scientific understanding, concomitant drug use, other life style factors and parental honesty regarding use during pregnancy. In the case of prenatal cannabis exposure, the currently existing three prospective observational studies only agree on one result, that prenatal cannabis exposure seems to predispose affected offspring to aggressive and impulsive behavior(57). Behaviour is hard to measure objectively and may also be affected by lifestyle factors.

1.3.3 ADRs in neonates - reaction characteristics

Neonates show different signs and symptoms of adverse drug reactions in comparison to older children and adults. The development of a child from conception to adulthood is dynamic, and changes in organ function and body composition affect pharmacodynamics and pharmacokinetics.

The retrospective review of Yellow Card reports in neonates between 2001 and 2010 showed the most common reactions to be rashes, erythema, bradycardia, convulsions and tachycardia, but whether or not this is an accurate reflection of the ADRs suspected in day to day practice is uncertain(6).

Belén Rivas et al reported feeding intolerance, phlebitis and tachycardia to be the most commonly suspected ADRs in their prospective study, with central hyperactivity, constipation and thrombocytopenia next most frequently reported with eight reports each. Whilst some of the serious reports in this study could be considered like those in adults, e.g. liver and renal failure, those that are neonate-specific are equally serious, such as necrotising enterocolitis. The parameters by which an ADR is defined will also differ in neonates compared to older children and adults. A heart rate of 64 beats per minute is within normal range for an adult but would be considered extreme bradycardia in a neonate and may be due to a drug, as suspected with morphine chloride(46). Table 2 outlines the results of three recently published papers which detail drugs documented to have caused ADRs in neonates.

Table 2 Number of ADRs by subtype seen in three studies

Clinical presentation	**Study**	**Total number of Neonatal ADRs reported in study**	**Proportion of ADRs with this clinical presentation reported**
General disorders + administration site disorders	*Kaguelidou 2016*	*3127*	*12.5% (391)*
Feeding intolerance	Rivas 2016	116	16.3% (19)
Local reaction	Hawcutt 2016	97	4.1% (4)
Malaise	Kaguelidou 2016	3127	1.5% (47)
Phlebitis	Rivas 2016	116	8.6% (10)
Blood and lymphatic system disorders	*Kaguelidou 2016*	*3127*	*11.9% (373)*
Anaemia	Rivas 2016	116	0.8% (1)
	Kaguelidou 2016	3127	2.9% (91)
Neutropenia	Kaguelidou 2016	3127	4.0% (128)
Thrombocytopenia	Rivas 2016	116	11.2% (13)
Cardiovascular disorders			
Bradycardia	Rivas 2016	116	0.8% (1)
	Hawcutt 2016	97	6.1% (6)
	Kaguelidou 2016	3127	1.9% (62)
Cardiac arrest	Hawcutt 2016	97	3.0% (3)
Hypertension	Rivas 2016	116	5.1% (6)

Clinical presentation	**Study**	**Total number of Neonatal ADRs reported in study**	**Proportion of ADRs with this clinical presentation reported**
Hypotension	Rivas 2016	116	0.8% (1)
	Hawcutt 2016	97	3.0% (3)
Tachycardia	Rivas 2016	116	8.6% (10)
	Hawcutt 2016	97	5.1% (5)
Respiratory disorders			
Bradypnoea	Rivas 2016	116	0.8% (1)
Decreased oxygen saturations	Hawcutt 2016	97	3.0% (3)
Dyspnoea	Hawcutt 2016	97	3.0% (3)
Gastrointestinal disorders	*Kaguelidou 2016*	*3127*	*8.1% (255)*
Constipation	Rivas 2016	116	6.8% (8)
Gastrointestinal haemorrhage	Rivas 2016	116	3.4%(4)
NEC	Rivas 2016	116	1.7% (2)
	Hawcutt 2016	97	3.0% (3)
Hepatobiliary disorders			
Jaundice	Rivas 2016	116	6.0% (7)
Liver failure	Rivas 2016	116	6.0% (7)
Renal and urinary disorders			
Renal failure	Rivas 2016	116	1.7% (2)
Nervous system disorders	*Kaguelidou 2016*	*3127*	*7.8% (245)*

Clinical presentation	**Study**	**Total number of Neonatal ADRs reported in study**	**Proportion of ADRs with this clinical presentation reported**
Central hyperactivity	Rivas 2016	116	6.8% (8)
Convulsion	Hawcutt 2016	97	5.1% (5)
Prolonged neuromuscular blockade	Rivas 2016	116	0.8% (1)
Metabolic disorders			
Hyperglycaemia	Rivas 2016	116	0.8% (1)
Lactic acidosis	Kaguelidou 2016	3127	2.1% (66)
Dermatological disorders			
Erythema	Hawcutt 2016	97	7.2% (7)
Pruritis	Hawcutt 2016	97	3.0% (3)
Rashes	Hawcutt 2016	97	14.4% (14)
Investigation results	*Kaguelidou 2016*	*3127*	*8.0% (251)*

1.3.4 ADRs in neonates - risk factors

A better understanding of the factors which may predispose a neonate to suffer an ADR would raise awareness in care teams and help to plan to prevent ADRs in those most vulnerable.

Although not neonate-specific, an international multicentre study conducted by Rashed et al. provided an insight into potential risk factors associated with ADRs in children. They concluded that age and gender are not associated with ADR incidence in children. Considerable commentary was provided on drug groups causing ADRs. Analgesics, anti-epileptics, antibacterials and antimycotics for systemic use, corticosteroids for systemic use and immunosuppressant agents (as classified by ATC classification) were defined as high-risk drugs in this study. These groups of drugs are all used in neonatal care. The number of high-risk drugs prescribed was higher per patient in those children experiencing an ADR compared to those children who did not. The prescription of three or more high-risk drugs was deemed a strong predictor of ADR occurrence, as was the prescription of five or more low-risk drugs (19). A study conducted in the 1970s found 29.6% of neonates in the NICU received five or more medications(21). It is likely this number has increased now due to the introduction of more drugs for neonatal care and more neonates surviving preterm birth.

As well as high numbers of drugs, literature reviews, cohort and control studies have suggested an increased incidence of ADRs in patients receiving unlicensed or off-label drug prescriptions (58–61). It has been estimated that up to 90% of neonates in a NICU may receive unlicensed or off-label drugs due to the lack of clinical trials including neonates(58)(62).

1.3.5 ADRs in neonates - current reporting practices

The UK pharmacovigilance system called the ‘Yellow Card Scheme’ was founded in 1964 by the MHRA and the Commission on Human Medicines after the tragedy of thalidomide left thousands of children with phocomelia. Since its introduction, the scheme has facilitated the spontaneous reporting of ADRs, which in turn has improved pharmacovigilance and thus influenced change in prescribing. However, despite these efforts, the suspected rate of underreporting for ADRs in all populations is estimated to be approximately 95%(7)(63)(64).

Until recent years, the MHRA requested the reporting of all ADRs in children, in contrast to reporting only those considered most serious and severe in adults. In September 2014, the MHRA published a ‘Drug Safety Update’ outlining updated guidance to only report ADRs in children that are considered to be ‘serious or result in harm’, but even prior to this change reporting was low(6). This change was in response to feedback regarding the impracticalities of reporting all ADRs in children(13). Comments on this change refer to the positive impact of

bringing paediatric advice in line with that of adults; combating reluctance to report and aiming to improve the quality and quantity of paediatric ADR reports(29).

The Yellow Card Scheme is not specifically designed for the reporting of ADRs suffered by neonates, and the need for a population-tailored method is apparent. The current scheme does not measure all outcomes needed to assess an ADR in this population. In the ten year period between 2001 and 2010, only 1% of 3496 ADR reports submitted for children less than two years of age recorded a gestational age, a factor that is understood to impact pharmacodynamics and kinetics(6). Some neonatal ADRs are being reported through the Yellow Card Scheme but to date no clinical warnings issued by the MHRA appear to have been influenced by those reports submitted in the UK(6).

The ADRIC research programme observed an increasing ADR risk with increasing age of the child. However, the investigators hypothesised the reason for this was multifactorial and confounded by underreporting. Neonates and young children cannot communicate their symptoms and thus ADRs such as pain and nausea can be difficult to recognise. Some signs and symptoms are dismissed as being normal characteristics of children of a certain age, such as vomiting or irritability in neonates(17).

1.4 Evaluating ADRs in neonates

Ideally, the identification, reporting and evaluation of ADRs in any population should be a routine part of day to day clinical care. Neonates are sufficiently different from older patients such that the key variables concerned with ADRs in this population may not be of importance in older children or adult populations, and hence a neonate-specific approach is desirable. Examples of the important variables in neonates include age and weight. Age is less important in mature adults but what is understood about pharmacokinetics and pharmacodynamics in preterm and term neonates suggests age to be of great importance for ADR evaluation in neonates. Weight in an adult is usually straightforward, but can be complex in neonates, including birth-weights, daily weights and working weights. The usual relationships in childhood between age and weight also break down, as in neonatal care weight and age are not always directly proportional.

A low threshold for suspecting and reporting ADRs in neonates is paramount to improving pharmacovigilance in this population. Suspected ADRs need to be evaluated in several ways including causality, severity and avoidability. There are many ways to do each of these evaluations.

1.4.1 Causality

Causality assessment is an important aspect of evaluating any ADR. The use of a causality assessment tool enables a structured and replicable assessment to be carried out which limits disagreements between assessors. Such tools may be used on an individual level by a suspecting clinician, but are also used by regulatory agencies such as the MHRA for the evaluation of ADR reports(65). Over 50 years ago Sir Austin Bradford Hill defined the aspects of association he considered to be important when evaluating the likelihood of causation, not specifically for ADRs, but for all biomedical topics(66). Whilst many causality assessment tools have been developed since these suggestions, few have been developed to be suitable for the paediatric population.

The Naranjo algorithm is a widely-used causality assessment method. In the ADRIC research programme however, it was concluded that the Naranjo algorithm was not suitable to be used to assess paediatric ADRs. Consequently a new tool was developed for children and when compared to the Naranjo algorithm showed greater inter-rater reliability(65). The Liverpool ADR causality assessment tool (LCAT) produced in ADRIC has not been assessed in neonates. A neonatal modification of the Naranjo algorithm was developed recently in one centre but this has not been validated in another site(67).

1.4.2 Severity

A clinician's decision to stop or reduce the dose of a drug causing an ADR may be affected by the severity of the ADR and a risk-benefit assessment. The team who conducted the ADRIC study used the Hartwig severity scale to assess the severity of the ADRs occurring in the paediatric inpatient population and those patients admitted due to an ADR. The team of investigators reported that whilst the Hartwig severity scale was easy to use, it may not be appropriate for assessing paediatric ADRs. In ADRIC's first study, a pilot study looking at ADRs causing admission to a paediatric hospital, the investigators deemed every child that was admitted to the hospital due to an ADR as 'needing treatment'. This meant that all ADRs were given a severity rating of at least 3, even if once the child had been admitted no active treatment or withdrawal of the suspected drug was actually needed(68).

Opinions regarding an ADR's severity will differ between clinicians, whether using assessment tools or not. The views of the patients experiencing them are also likely to be different in many cases. This difference could be even more profound in the paediatric population who may be easily distressed by the effects of an ADR, and in their parents who stand witness. ADRIC recognised this in a larger inpatient study and subsequently investigated parent views on ADRs(17,69).

The severity of ADRs may not be entirely apparent in neonates, making this hard to assess. Some long-term effects may not appear until several years after the event. A severity score for assessing ADRs in neonates has recently been developed by the International Neonatal Consortium but has not yet been validated in any population.

1.4.3 Avoidability

Assessing the avoidability of an ADR contributes to clinician education, overall assessment of case management and the evaluation of different treatment options. Hartwig also developed a preventability questionnaire consisting of four questions(70). The ADRIC research programme used the Hallas scale of avoidability in the pilot study and found 33% of the ADRs causing admission to hospital 'possibly avoidable', though none could be deemed 'definitely avoidable'. The team of investigators thought the classifications in the tool were too broad. In the larger study of ADRs causing paediatric admissions just over one fifth of the ADRs were deemed to be definitely or possibly avoidable, and this figure increased when analysing only the ADRs not associated with oncology patients(18). The decision was made in the inpatient ADRIC study not to assess avoidability of the ADRs due to the absence of an appropriate tool suitable to assess the cases(17). As a result of this research programme, a paediatric avoidability tool was developed. Whilst the tool was designed to be appropriate to use to assess paediatric ADRs, its use is not limited to the paediatric population. It has not yet been validated in neonates(71).

1.5 Conclusion

In conclusion, the identification and evaluation of ADRs in neonates, with the aim of improving the safety of medicines, is far behind the standard in older populations. The pharmacokinetics and pharmacodynamics exhibited by neonates differ to those in older children and adults. Therefore, neonates require their own medicines and will exhibit different ADRs, but the practice of monitoring the side-effects of medicines is haphazard and is not influencing change. The current method of reporting ADRs does not collect all the information needed to assess a neonatal ADR and thus the rate of underreporting seen using currently available methods is substantial. This is unsatisfactory for several reasons. Despite the legal initiatives that aim to encourage further work, the lack of research into medicines for neonates means many will receive unlicensed or off-label medicines for which there is little information about safety. Because of this, ADR reporting in this vulnerable population should take an even higher priority. ADRs are an important health problem which cost significant money, but the lack of pharmacovigilance, both in routine practice and research, means knowledge about neonatal ADRs is lacking. What is beginning to be understood is that the incidence of ADRs in neonates is significant, they are characteristically different to those in adults, and occur because of

different risk factors and drugs from different sources. To increase understanding, the evaluation of neonatal ADRs that are identified is very important, but less research has been done into how to do this in neonates. There are multiple tools to use for this but very few are designed for paediatric populations, and adult tools have rarely been tested for their use in children or neonates. The use of inappropriate assessment tools could be leading to the generation of inaccurate and unreliable data. It is important that pharmacovigilance research now expands to include optimising the evaluation of neonatal ADRs, as well as their identification.

1.6 Aims and objectives

In order to address the issues outlined above, the aim of this study was to improve the understanding and assessment of neonatal ADRs.

In order to meet this aim, the study set the following objectives

Primary objective:

To generate prospective neonatal ADR data to allow the comparison of several causality tools in the neonatal setting

Secondary objectives:

a) To make preliminary estimates of the frequency and incidence of ADRs in neonates admitted to the NICU at Liverpool Women's Hospital over a nine-week period
b) To describe the ADRs occurring in the neonatal population
c) To consider how reporting of ADRs in a neonatal setting may be improved including trialling a neonate-specific surveillance system

Chapter 2: Systematic review protocol

In the early stages of the project, a protocol for a systematic review of ADRs in neonates was developed and can be found below. The search strategy was tested in four databases and the results found in the search at the end of 2016 are included below.

2.1 Objectives

Primary:

a) To investigate the characteristics of adverse drug reactions that occur in neonates

Characteristics will be defined by recording the following data from studies:

- Clinical presentation of the ADR
- Corrected gestational ages of neonates at time of experiencing ADRs
- Gestational ages at birth of neonates experiencing ADRs
- Weights of neonates at time of experiencing ADRs
- Birth-weights of neonates experiencing ADRs
- Risk factors considered for neonates developing ADRs
- Outcomes of ADRs
- Severity of ADRs

b) To investigate which drugs most commonly cause adverse drug reactions in neonates

Drugs will be defined by recording the following data from studies:

- Name of drug
- Class of drug (by Anatomical Therapeutic Chemical classification)
- Unlicensed/off-label status
- Route of administration
- Concomitant medications

Secondary:

a) To investigate the frequency/incidence of adverse drug reactions in neonates as reported in previous studies

2.2 Review question development

The following concepts were considered when designing the research question for this systematic review

Adverse drug reactions in neonates			
Concept 1	**Concept 2**	**Concept 3**	**Concept 4**
Neonates	Adverse drug reactions	Pharmacological interventions	Observational studies

2.3 Evidence gathering and study selection

2.3.1 Evidence gathering

There will be four techniques used for gathering evidence

- Database searching

  Databases may be searched using a pre-determined strategy (table 3) searching all fields available

- Contact with experts

  Experts in the field of ADRs in neonates will be contacted via email to discuss access to any published or unpublished work not returned by the database search for use in the review

- References searching

  Following on from database searches the references of relevant papers will be searched in order to identify any potential papers not returned by the original database search

All identified literature will be exported for online storage via Mendeley referencing software. This will aid with the exclusion process and management of references during the review.

2.3.2 Eligibility criteria

- Types of studies

  Included studies: observational studies studying ADRs in neonates including both retrospective and prospective studies in any setting

Studies will be eligible from any year of publication from any country of publication

Observational studies studying ADRs in a larger paediatric population where it is possible to define the included neonatal population and data is provided on the neonatal population alone will also be included

Excluded studies:

Observational studies looking at ADRs in a paediatric paper where it is *not* possible to define the included neonatal population and/or data is not provided on the neonatal population alone

Studies not written in English will only be excluded once reasonable effort has been made to obtain a translation

- Types of participants

  Neonates in any setting- neonates born premature will be included in the review however neonates more than 28 days post their estimated date of delivery will be excluded. This definition will allow for the inclusion of neonates born preterm.

- Types of interventions

  Adverse drug reactions to any medication, including aromatherapy, homeopathy and natural/herbal remedies. This will include exposure to drugs pre-conception, in pregnancy, during labour and through breast feeding.

  Any clinical event which meets the definition of an ADR used in this review as defined by Allegaert et al as ‘an unintended and harmful effect resulting from the use of medications intended for diagnostic or therapeutic reasons (irrespective of the dose)’(10).

2.4 Paper exclusion and data extraction

2.4.1 Paper exclusion method

Review at title level:

- Exclude if does not study human participants
- Exclude if does not include any of the concept 1 synonyms in the title
- Exclude if does not include any of the concept 2 synonyms in the title

Review at abstract level:

- Exclude if not deemed relevant to review i.e. the keyword relating to concept 3 should refer to a pharmacological intervention and not any other kind of intervention e.g. surgical or procedural

Review at full publication level:

- Does the paper study a population as defined by ‘babies born at any gestation who are not more than 28 days post their estimated date of delivery’- exclude if this population is not studied or if it is not possible to extract data on this population alone if included in a larger paediatric population

Reasons to exclude at the abstract and full publication stage will be will be documented. A sample of 10% of the excluded papers will be reviewed by the supervisor using the above methods to ensure valid exclusion has taken place by the research student. Any disagreement will be followed up involving a third reviewer if necessary. Any papers with uncertain inclusion or exclusion will be reviewed by the educational supervisor(s) and decided by discussion between the research team.

2.4.2 Data extraction

Following the identification of appropriate literature, each paper will be summarised and evaluated using a predefined paper evaluation form. Data will be extracted using a data extraction form created by the researcher to enable relevant data extraction.

The following data will be extracted for each study meeting the inclusion criteria:

Study characteristics:

- Country
- Year conducted
- Duration
- Number of sites
- Design
- Clinical setting
- Number of neonates
- Whether neonates included as part of larger paediatric population

Identification of ADR:

- Definition of ADR used
- Definition of drug exposure used (included details of whether maternal/paternal exposure and breast feeding were considered)
- Incidence definition and calculation (if included)
- Details of any causality assessments carried out
- Details of any severity assessments carried out
- Details of any avoidability assessments carried out
- Who conducted the assessments
- Methods used to identify and report ADRs

Information relating to the ADR:

- Clinical presentation
- Associated drugs/drug classification
- Associated risk factors identified

Once this data has been extracted it will be stored on a password-controlled predesigned spreadsheet on a University or personal computer.

2.4.3 Assessment of methodological quality of included studies:

In a recent research programme conducted in Merseyside (the Adverse Drug Reactions in Children programme), a quality assessment form for critically appraising observational studies of adverse drug reactions was created specifically for the systematic review. This form will be used in this new systematic review. It takes into consideration study design, ADR identification method and causality, severity and avoidability assessments(4).

2.5 Dissemination

Results of this systematic review will be:

- reported to Trust bodies
- presented at regional meetings
- submitted to MHRA
- submitted for publication by peer-reviewed journals.

Table 3 Pre-determined search strategy for systematic review

Pre-determined search strategy
Concept 1 1. neonat* 2. Exp neonate 3. Exp newborn 4. (neonat* or newborn* or new born* or new-born* or baby or babies) 5. Exp child 6. Exp adolescent 7. (young adj 2 (person* or people or adult* or individual* or women or woman or men or man)).ti,ab. 8. Exp student* 9. Puberty/ 10. Paediatrics/ 11. Pediatrics/ 12. (infan* or child* or schoolchild* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or minor* or juvenile* or youth* or kindergar* or nurser* or puber* or prepuber* or pubescen* or prepubescen* or pre pubescen* or paediatric* or pediatric* or schoolage*).ti,ab.
Concept 2 1. side-effect*.ti,ab. 2. Side effect*.ti,ab. 3. (drug induced or drug related or drug safety).ti,ab 4. tolerability.ti,ab. 5. harm*.ti,ab. 6. adrs.ti,ab. 7. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab 8. (toxic adj3 (effect* or reaction* or event* or outcome*)).ti,ab 9. exp product surveillance, postmarketing or exp adverse drug reaction reporting systems or exp drug toxicity or exp abnormalities, drug induced or exp drug hypersensitivity
Concept 3 1. (drug* or pharmaceutical* or medicin* or intervention*).ti,ab. 2. pharmaceutical preparations

3. (herbal* or plant* or herb* or aromatherap* or aroma therap* or homeopath*).ti,ab.
4. Medicine, Chinese Traditional/ or Plant Preparations/ or Plants, Medicinal/ or Plant Extracts/ or Drugs, Chinese Herbal/
5. Aromatherapy

Concept 4

1. Health Care Surveys
2. Retrospective studies
3. Prospective studies
4. Cohort studies
5. Observational stud*.ti,ab.
6. (prospectiv* adj3 review*).ti,ab.
7. (prospectiv* adj3 stud*).ti,ab.
8. (retrospectiv* adj3 review*).ti,ab.
9. (retrospectiv* adj3 stud*).ti,ab.
10. population-based stud*.ti,ab.
11. cohort stud*.ti,ab.
12. incidence stud*.ti,ab.
13. Sn.fs
14. Epps's
15. monitor*.ti,ab.
16. Surveillance.ti,ab.

Table 4 Test run of search strategy using four databases

Scopus original articles returned: 11,076	**PubMed** original articles returned: 5227	**ScienceDirect** original articles returned: 1,372	**Web of Science** original articles returned: 27
Scopus articles after article type limitations applied: 10,750	PubMed articles returned after article type limitations applied: 5205	ScienceDirect articles returned after article type limitations applied: 1,372	Web of Science articles returned after article type limitations applied: n/a
Scopus articles after duplicates removed: 10609	PubMed articles after duplicates removed: 5199	ScienceDirect articles after duplicates removed:1353	Web of Science articles after duplicates removed: 24
Total number of combined articles: 17185			
Total number of combined articles after duplicates removed: 12289			
Remaining papers after exclusion at title level:			
Remaining papers after exclusion at abstract level:			
Remaining papers after exclusion at full paper level:			
Final number of papers (including re-inclusion papers):			

Chapter 3: Methodology

Due to the highly demanding and emotive nature of neonatal care, ADR reporting is often overlooked in day to day practice. There is an aspect of educated guesswork in neonatal prescribing due to the lack of inclusion of children, infants and neonates in drug trials, and so thorough pharmacovigilance in this population should be a part of good clinical practice. Though the benefits of improving reporting are clear, it is important to consider the costs too. There are financial costs of introducing new protocols, resources and jobs but also costs to the workload and morale of staff and families already facing a difficult experience.

To be able to generate prospective neonatal ADR data, careful consideration of methodology to effectively identify, record and evaluate neonatal ADRs was needed. Proposed methods needed to be effectively integrated into neonatal care, whilst utilising the addition of an independent researcher. To begin to understand how reporting and evaluating ADRs in neonates can be improved, this study trialled the implementation of a neonate-specific ADR data collection proforma, used by a standalone researcher prospectively observing for neonatal ADR cases. These cases were then used to evaluate causality assessment tools to determine their use for assessing neonatal ADRs.

3.1.1 Study setting

This study was conducted at the University of Liverpool and the clinical site of Liverpool Women's Hospital, Richard Cooke Neonatal Unit. The unit is a tertiary neonatal unit with 44 cots; 12 for intensive care, 12 for high dependency care and 20 for low dependency care. The unit treats neonates born prematurely or with medical or surgical conditions requiring treatment from the North West of England, North Wales, Isle of Man and the rest of the UK(1).

3.1.2 Study introduction

From October 2016, the researcher attended the neonatal unit and the daily ward rounds and handovers to introduce the study to the NICU staff. Efforts were made to introduce the study to the majority of staff individually, who were encouraged to ask questions. Advice was sought from the unit's neonatal research nurses who helped in the introduction and advised effective ways of disseminating information regarding the study.

In addition to this, the study was formally introduced to staff with a presentation and Q&A session at the following meetings:

Senior nurse meeting: 11th October 2016

Clinical Governance Day: 22nd November 2016

Consultants meeting: 29th November 2016

These formal presentations were in addition to informal day to day conversations with ward staff and posters and flyers about the study displayed in staff areas. Staff include Health Care Assistants (HCAs), neonatal nurses, advanced neonatal nurse practitioners (ANNPs), junior doctors, consultants, researchers and pharmacists.

3.1.3 Study materials design

To begin data collection, it was necessary to create a data collection proforma to collect all the information needed to reliably evaluate a neonatal ADR.

The creation of the data collection proforma took several weeks and several versions were adapted before the final version was reached. Firstly, all fields that are included in a Yellow Card report form were outlined. Some required adaptation to enable the collection of neonate-specific data, such as age and weight. Other areas were expanded upon to collect further relevant information, for example, extra fields added into medical history to ensure information was also collected regarding labour, pregnancy and maternal history. The 'Council for International Organisations of Medical Sciences' suspected adverse reaction report form, which is frequently used to report ADRs occurring in clinical trials, was also consulted and additional fields added to the data collection proforma.

Following this, the proforma was discussed with neonatal consultants, nurses and research nurses, as well as the pharmacists who worked on the ADRIC project. Further adaptations were made to the proforma following their suggestions, many of which were regarding the usability of the tool, for example, how to record changes in laboratory investigations.

Finally, when the three causality assessment tools that were to be evaluated had been decided upon, these were reviewed to make sure the data collection proforma would collect all the information necessary to use these tools. Some fields were added for this, for example, a field prompting commentary on the existence of any positive re-challenges or histories.

The method of identifying neonatal ADRs, using the data collection proforma when attending NICU ward rounds and following up cases from patient notes, was piloted during October and November 2016. Further adjustments were made to the proforma following the piloting of the data collection. Version 9.0 was used as the final version in the study, a copy of which can be seen below. The proforma was converted into an excel spreadsheet to enable the inputting of data directly into the computer where possible.

An 'ADR alert form', for use by any NICU member of staff to alert the researcher to suspected ADR cases, was also designed. This can be found in appendix 2.

PART A + B: PATIENT DETAILS AND MEDICATION HISTORY

Part A: PATIENT DETAILS			
ADRIN number		**Gender**	female
Post-natal age (hours or days)			
Gestational age at birth (in weeks and days)			
Birth weight (grams)			
Weight at time of event (grams)			
Was this a multiple pregnancy?		If yes, please state number of babies:	
Date (on day ADR suspected)			

PART A + B: PATIENT DETAILS AND MEDICATION HISTORY

Part B: MEDICATION HISTORY please give details of all medications prescribed to the patient in the 72 hours preceding the suspected ADR including those suspected to have caused ADR					
Drug	**Route**	**Dose**	**Date started**	**Date stopped**	**Indication**

PART C: SUSPECTED DRUGS

Part C: SUSPECTED DRUGS							
Drug	**Route**	**Dose**	**Date and time started**	**Date and time stopped**	**Indication**	**Source (prescribed to baby, prescribed to breast feeding mother, prescribed to mother in labour, prescribed to mother in pregnancy, prescribed to mother or father pre-conception)**	**Was the suspected drug prescribed: a) unlicensed or b) off-label?**
Had this drug(s) been given to this patient in a different dose(s) or route(s) previous to the suspected ADR? Y/N *If yes*, please provide details of doses/routes and dates given below:							

PART D: SUSEPCTED REACTION DETAILS

Part D: SUSPECTED REACTION DETAILS				
DESCRIPTION OF EVENT				
Clinical signs and symptoms:				
Change in observations:				
	First recorded value following time ADR first noticed	Highest recorded value following time ADR first noticed	Lowest recorded value following time ADR first noticed	Is this change likely to be related to the suspected ADR? If no, please give alternative reason for change
Heart rate				
Respiratory rate				
Temperature				
Blood pressure (please state whether mean or alternative)				
Blood glucose				
Urine output				
Hero score				
Other (please state)				

PART D: SUSEPCTED REACTION DETAILS

Change in investigations noted: e.g biochemistry, haematology, imaging etc (if applicable)

Investigation name	First recorded value following time ADR first noticed	Highest recorded value following time ADR first noticed	Lowest recorded value following time ADR first noticed	What are the likely explanation(s) for this change in observation?

What changes were made to the suspected causative drug? (please tick)

Continued ☐	
Dose changed ☐	New dose:
	Date and time dose changed:
Stopped and substituted ☐	Drug substituted with:
Stopped and not substituted ☐	
Discontinued for reason other than ADR including if stat dose only ☐	

What happened after the changes were made?

	Details
Improvement of clinical condition/observations/investigations ☐	
No change of clinical condition/observations/investigations ☐	
Deterioration of clinical condition/observations/investigation ☐	
Unknown ☐	

PART D: SUSEPCTED REACTION DETAILS

Date and time reaction first noted:	
Date and time of first evidence of reaction:	
Date and time reaction noted to be improving (if applicable):	
Date and time reaction noted to be resolved (if applicable):	
Was any treatment given? If drug(s) given, please record below	

Was there a re-challenge? If yes, please provide details including date and time of re-challenge and outcome
Is there a history of this patient suffering the same reaction to this drug before? If yes, please provide further detail

Drug	Dose	Route	Date and time started	Date and time stopped	Indication

What was the outcome of the reaction?	Other (please give details)	**Was escalation to a higher level of care required? If yes, please give details**	Yes ☐	No ☐	Baby already on ITU ☐
	Details:		From:	To:	
		Type A or type B reaction?	Type A ☐	Type B ☐	Unknown ☐

Underlying clinical problems/differential diagnosis for suspected ADR:

PART E: FURTHER CLINICAL DETAILS

Part E: FURTHER CLINICAL DETAILS					
Any significant events preceding reaction e.g. surgery, general anaesthetic					
Is/was this patient receiving mechanical ventilation? If yes please provide details					
Ongoing medical or surgical conditions including any congenital anomalies					
Is/was the patient receiving mother's breast milk?	*If yes,* please provide any details of medications taken by breastfeeding mother below		*If no* , please state method of current feeding e.g. Donor EBM, TPN, oral feeds		
Drugs taken by breastfeeding mother (prescribed, OTC, herbal and recreational)					
Drug	Dose	Route	Date and time started	Date and time stopped	Indication
APGAR scores at birth	1 minute ☐		5 minutes ☐	10 minutes (if recorded) ☐	
Condition at birth:					
Resuscitation required:					
CRIB II score recorded in first 24 hours					

PART E: FURTHER CLINICAL DETAILS

Nature of birth					
Mode of delivery ✓	Vaginal				
Was the labour induced?					
Complications in labour:					
Drugs given in labour					
Drug	Dose	Route	Date and time started	Date and time stopped	Indication
Drugs given in pregnancy (prescribed, OTC, herbal and recreational)					
Drug	Dose	Route	Date and time started	Date and time stopped	Indication
Any other significant pregnancy history					
Any other significant maternal medical history including drugs given pre-conception					
Maternal age at date of delivery		**Gravidity**		**Parity**	

REPORTING DETAILS	
Recorded by	
Alerted to ADR by	
Information source e.g. patient notes, clinician account	
Date recorded	
Date yellow card completed	

3.2 ADR case collection

3.2.1 Participants

Neonates admitted to the neonatal unit between 30th January and 31st March 2017 were considered for inclusion in the study. Neonates were eligible provided they were no more than 28 days post-term for corrected gestational age at the time of recruitment to the study. This included neonates who were already inpatients on the unit when the data collection period began. Although previous studies have collected data on all neonates or children admitted to a unit, this study only recruited and collected data on neonates who were suspected to have suffered an ADR. This decision was made because the study aimed to compare causality assessment methods and this required detailed ascertainment of the course and outcome of neonatal ADR cases. Although data was not collected regarding those neonates not experiencing an ADR, the researcher kept brief anonymised handwritten notes regarding the ongoing care of each neonate for record should they later experience a suspected ADR.

A formal sample size calculation was not performed as this study was an exploratory analysis rather than a hypothesis test, and the project was time-limited. To characterise tools used to evaluate suspected ADRs in neonates, the study needed to collect enough suspected ADR cases. Previous work has used between 50 and 100 cases of ADRs to do this(65)(67).

3.2.2 ADR case data collection

The data collection period was nine weeks long from 30th January to 31st March 2017. The daily NICU handover and ward round were attended by the researcher four times a week, usually Monday, Tuesday, Thursday and Friday. On these four days, the ward round for the intensive care cots was monitored three times and the ward round for the high-dependency and low-dependency beds once. The unit also has eight transitional care cots but these were not monitored.

The purpose of attending the daily handover and ward round was to allow the researcher to monitor the care of the neonates on the NICU, focussing on drug prescription and possible symptoms of ADRs. During the ward round the researcher could listen to staff conversation, ask questions and review drug charts.

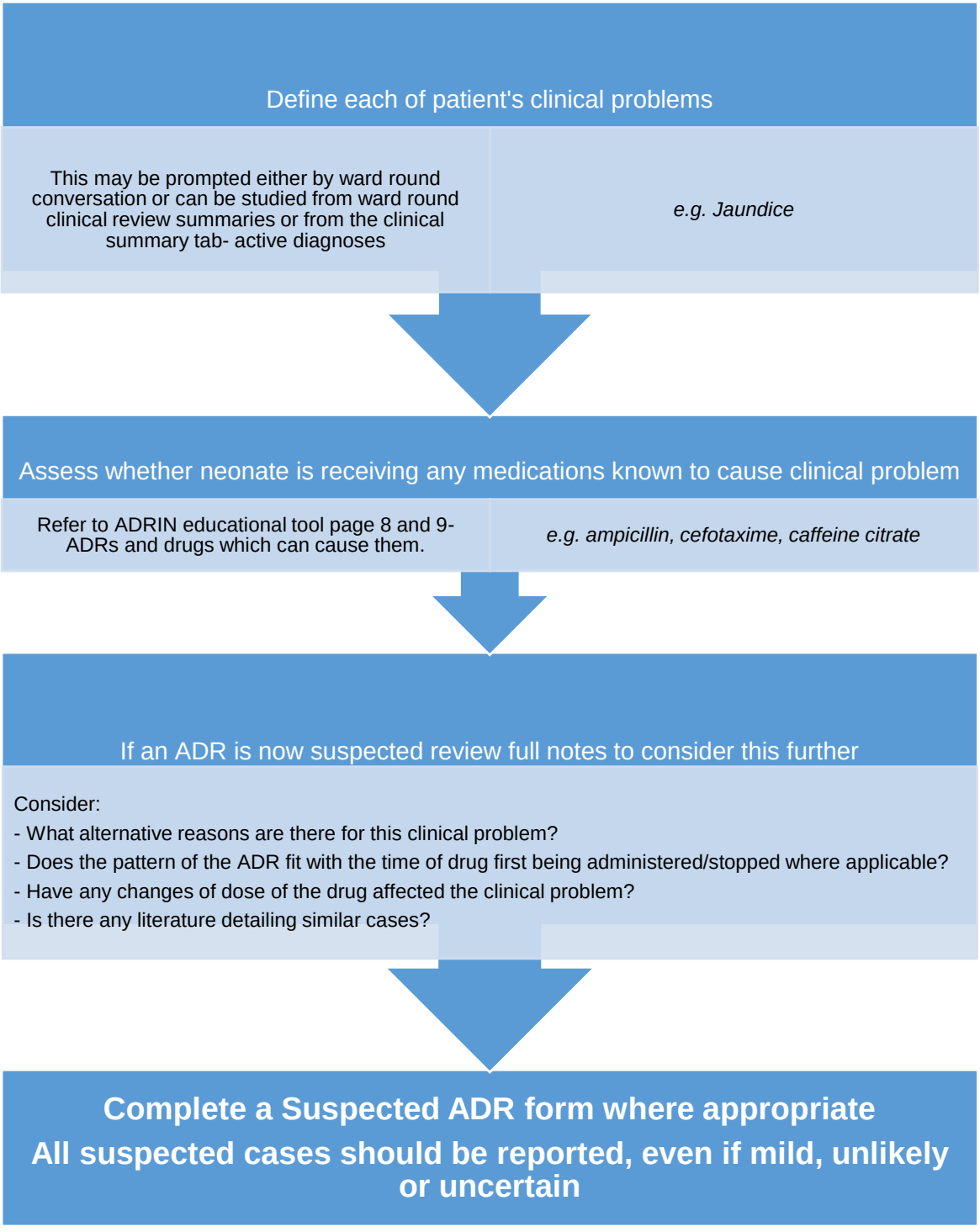
Following the ward round a daily structured review was undertaken of neonates' notes on BadgerNet, the electronic patient notes database used on the LWH NICU. An outline of the steps undertaken in a structured review can be found below. The notes of neonates suspected to be suffering from an ADR were reviewed first and other notes reviewed with any remaining time.

Structured review guidelines

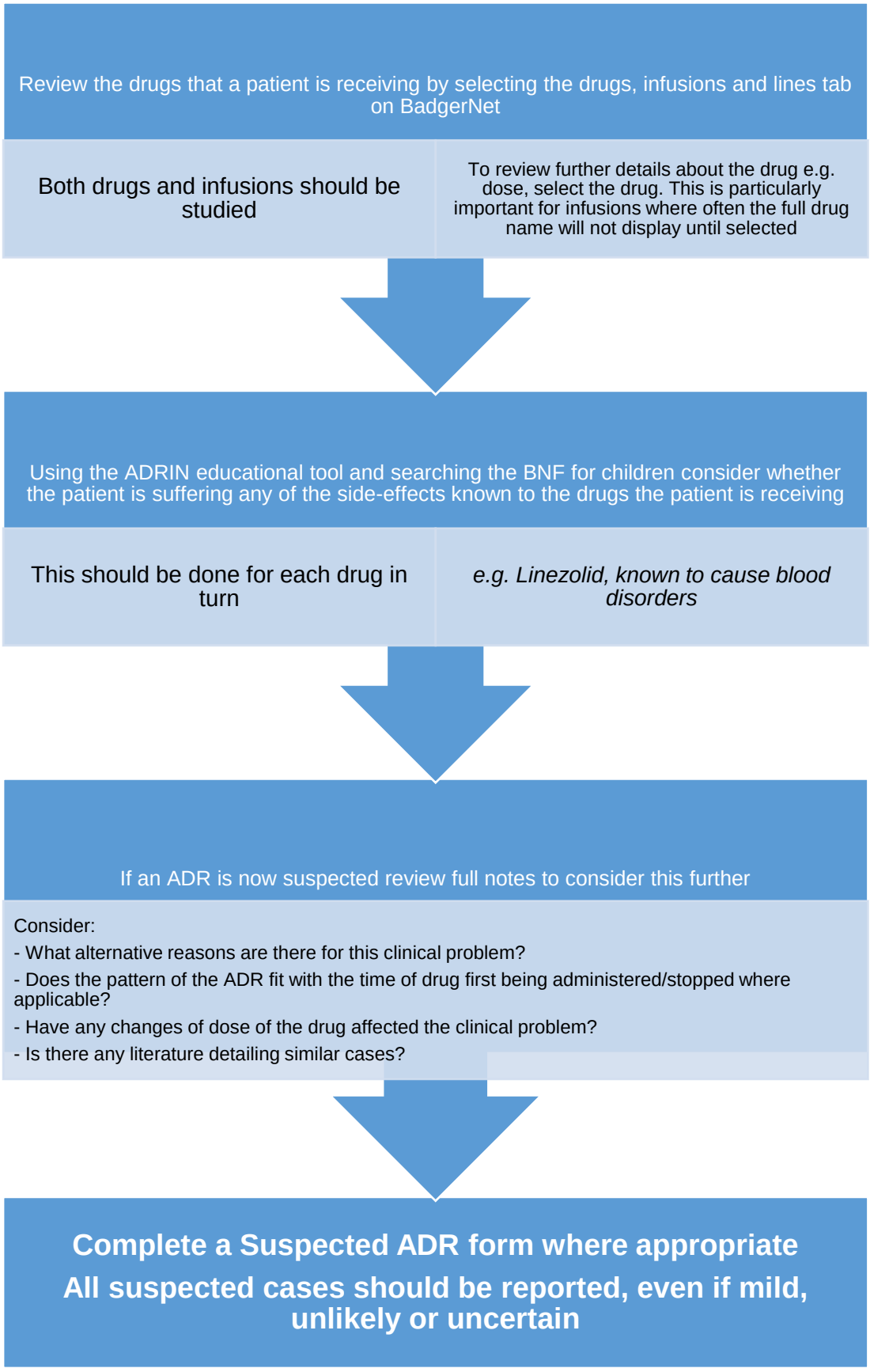
COMPLETING A DAILY STRUCTURED CLINICAL REVIEW OF A NEONATE

Following attendance at either ITU/HDU ward round a structured clinical review of neonates' notes should be undertaken. This document provides guidance on how this may best be done.

Step 1: problem focussed:



Step 2: drug focussed



To improve the detection of ADRs in neonates, time was spent piloting the study, and reading about common neonatal ADRs and previous research in this area. An educational tool was also developed outlining details of neonatal ADRs; common ADRs, serious ADRs, ADRs from frequently used medicines on the NICU, drugs causing ADRs unique to neonates, ADRs from antibiotics and anti-fungals, drugs known to cause extravasation injuries and off-label and unlicensed drugs prescribed on the unit. This educational tool was used for reference at all ward rounds. The British National Formulary for children online (BNFc) was consulted for any further information required.

In addition to researcher ward presence, 'ADR alert forms' were available to all staff to complete where necessary. These allowed staff to alert the researcher to any suspected ADRs in a neonate they were caring for. Staff were encouraged at regular intervals throughout the data collection period to complete these forms for all suspected ADRs, regardless of perceived severity and causality, and they were reassured that any reported suspicions would be further analysed by the study team. These forms were placed inside the drug information folders used by staff when prescribing and administering drugs. These folders were checked on a regular basis by the researcher for any completed forms.

If an ADR was suspected for any neonate a 'Suspected ADR in a Neonate' data collection proforma was completed by the researcher for each ADR case. Each case was entered directly into the password-protected spreadsheet version of the data collection form and stored securely on a university computer. Parental consent was not taken to recruit the neonate to the study as the information collected was considered routine data monitored as part of daily care. Parents were not informed that the study was being undertaken, but staff members were briefed to answer any parents' questions by explaining that drug safety is routinely monitored on the unit as part of the care provided. Each neonate who was suspected to have suffered an ADR was given a study number and a paper copy only of the study numbers and corresponding neonate hospital numbers was kept in a locked drawer in the card or code access only research department of the Institute for Women's and Children's Health located at the Liverpool Women's Hospital site.

Once a case report was collected for a suspected ADR, the ADR in question was followed up for a minimum of two weeks. If the clinical sign or symptom had resolved or improved by the two-week point, the outcome was recorded as 'improvement of clinical symptoms/observations/investigations'. If the clinical sign or symptom had not improved by this point, it continued to be monitored until either the reaction resolved/improved, the outcome of 'no change in/deterioration of clinical symptoms/observations/investigations' could be

justified, or the neonate was discharged. This methodology was decided upon as this was a single investigator study with limited time.

In this study, the decision was made to collect and report data regarding any suspected ADRs regardless of their severity and previously published information. This aimed to maximise the opportunity to observe neonatal ADRs for a continuous time and to provide a wide range of cases for the comparison of causality assessment tools.

Once the data collection period had finished, Yellow Card reports were submitted to the MHRA for all cases that were given a probable or definite causality rating by the principal investigator using the Liverpool ADR Causality Assessment Tool.

3.2.3 Drug inclusion and exclusion

Reactions to any drugs prescribed to any neonate on the neonatal unit were included in this study, regardless of licensing or label status. Drugs causing ADRs were classified into groups using the Anatomical Therapeutic Chemical (ATC) classification method designed by the WHO Collaborating Centre for Drug Statistics Methodology(72). Using this classification, drugs were classified by first and second order classifications only. The licensing and labelling statuses of the drugs were confirmed by checking the Summary of Product Characteristics via the EMA website, and discussing any queries with a senior member of the research team. Drugs prescribed to the neonate when in any other ward or hospital were not included. This includes drugs prescribed to the neonate when on the labour ward, e.g. resuscitation drugs.

Blood products, except for immunoglobulins, were not included. Enteral feeds, including infant formulas, were not classified as drugs in this study. Drugs that were used by the father or mother preconception or by the mother during pregnancy, labour or breastfeeding were also included if they resulted in a neonatal ADR, but the information regarding the doses and prescription of these drugs was sometimes limited. Recreational drugs were included in this study but the classification and quantification was more difficult. Recreational drugs refers to the use of illegal and legal drugs without medical supervision, as defined and described in the British Medical Journal(73). It covers four main categories of drugs; analgesics, depressants, stimulants and hallucinogens(73).

3.2.4 ADR definition

The ADR definition used in this study was that by Allegaert et al as ‘an unintended and harmful effect resulting from the use of medications intended for diagnostic or therapeutic reasons (irrespective of the dose)’(10). This definition was considered the most appropriate for this study as it enables the inclusion of drugs that are unlicensed or off-label by discounting dose as a factor. Reactions that had begun before the first day of data collection were included

providing the reaction was still occurring when data collection commenced. Medication errors were not included in this study as the focus was to be on adverse drug reactions occurring under correct prescribing, and a large study surveying medication errors had recently taken place on the unit.

3.3 Comparison of results to Yellow Card reports to the MHRA

To further evaluate the ADRs reported in this study, the collected cases were compared to neonatal ADRs that were reported to the MHRA in a different time set. This was done by analysing a paper by Hawcutt et al that described all the neonatal ADR reports to the MHRA between 2001 and 2010(6). The results outlined in this paper were compared to the results of this prospective observational study. Comparisons were made between the frequency and rate of reporting, gender of neonates, reaction types reported and drugs suspected. The two sets of results were tabulated for comparison.

3.4 Causality assessment process

Following the data collection period, causality assessments were performed by multiple assessors on a sample of the total cases. The sample was chosen by including only one case of an ADR where there were multiple cases of similar ADRs, and not including ADRs caused by parental drug use. This process aimed to assess the use of three different currently existing causality assessment tools.

3.4.1 Three compared methods

Karch and Lasagna algorithm

It was decided to assess the Karch and Lasagna algorithm following its use in a recent prospective observational study into adverse drug reactions in neonates, conducted in Spain by Belén Rivas et al (46). The exact version of the tool that was used in the study was obtained and translated into English. The algorithm was developed in the 1970s. Karch and Lasagna recognised that categorising and evaluating ADRs depended on the clinical judgement of clinicians, which varied between individuals. Their proposed definitions for ‘definite’, ‘probable’, ’possible’, ‘conditional’ and ‘unlikely’ ADRs aimed to encourage more objective evaluation of ADRs and define ‘tolerance limits’ for the unavoidable variation in clinician opinion(74)(75).

Scoring of the algorithm of the Spanish Pharmacovigilance system

A. Temporal sequence

- Compatible + 2
- Compatible but not coherent + 1
- No information 0
- Incompatible -1
- ADR appears on withdrawing/withholding medicine -2

B. Previous Knowledge

- ADR well known, +2
- ADR known (occasional references), +1
- ADR unknown, 0
- Information against the connection, -1

C. Effect of the withdrawal from medicine

- ADR improves, +2
- ADR doesn't improve, -2
- They don't withdraw the medicine and ADR doesn't improve, +1
- They don't withdraw the medicine and ADR improves, -2
- There isn't information, 0
- ADR fatal or irreversible, 0
- They don't withdraw medicine, ADR improves by tolerance/ resistance, +1
- They don't withdraw medicine, ADR improves by treatment, +1

D. Return of ADR after re-exposure to the drug

- Positive: ADR appears, +3
- Negative: ADR doesn't appear, -1
- There isn't re-exposure or sufficient information, 0
- ADR fatal or irreversible, 0
- Similar previous reaction with another pharmaceutical speciality/specialisation, +1
- Similar previous reaction with another drug, +1

E. Existing/ Existence of alternative causes

- A more plausible alternative explanation, -3
- An equal alternative explanation -2
- Or less plausible, -1
- There isn't information that establishes this, 0
- There isn't sufficient information that dismisses this, +1

F. Contributing factors which favour the causal relationship, +1

G. Extra Examinations (serum levels of medicine, biopsies, radiological examinations, allergic testing, etc.), +1

A+B+C+D+E+F+G = Causal Relationship

- Unlikely, ≤0
- Conditional, 1-3
- Possible, 4-5
- Likely, 6-7
- Definite, ≥8

New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units (Du Lehr)

The ‘New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units’ (referred to here as the Du Lehr algorithm) was designed by Wei Du et al at Wayne State University, Detroit, USA. The team aimed to create an ADR causality assessment tool that would be suitable and specific to the neonatal population. They recognised the increased risk of ADRs in critically ill neonates in intensive care receiving multiple different medications, and that existing algorithms often disagree with the opinions of experts. They hoped their tool would apply consideration to the impact of underlying disease and polypharmacy as well as weighting the contributions of different factors. The algorithm was created by comparing experts’ classifications of a sample of real neonatal ADR cases with their assessments using a new 24 item questionnaire. Statistical analysis of the classifications resulted in removal of some questions, so that the final product is a 13-item questionnaire with weighted scoring for yes, no or not applicable answers. The questionnaire was validated using a further 50 prospectively collected neonatal ADR cases, but as far as is known at present, has not been further validated outside of this setting(67).

New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units (Du Lehr)

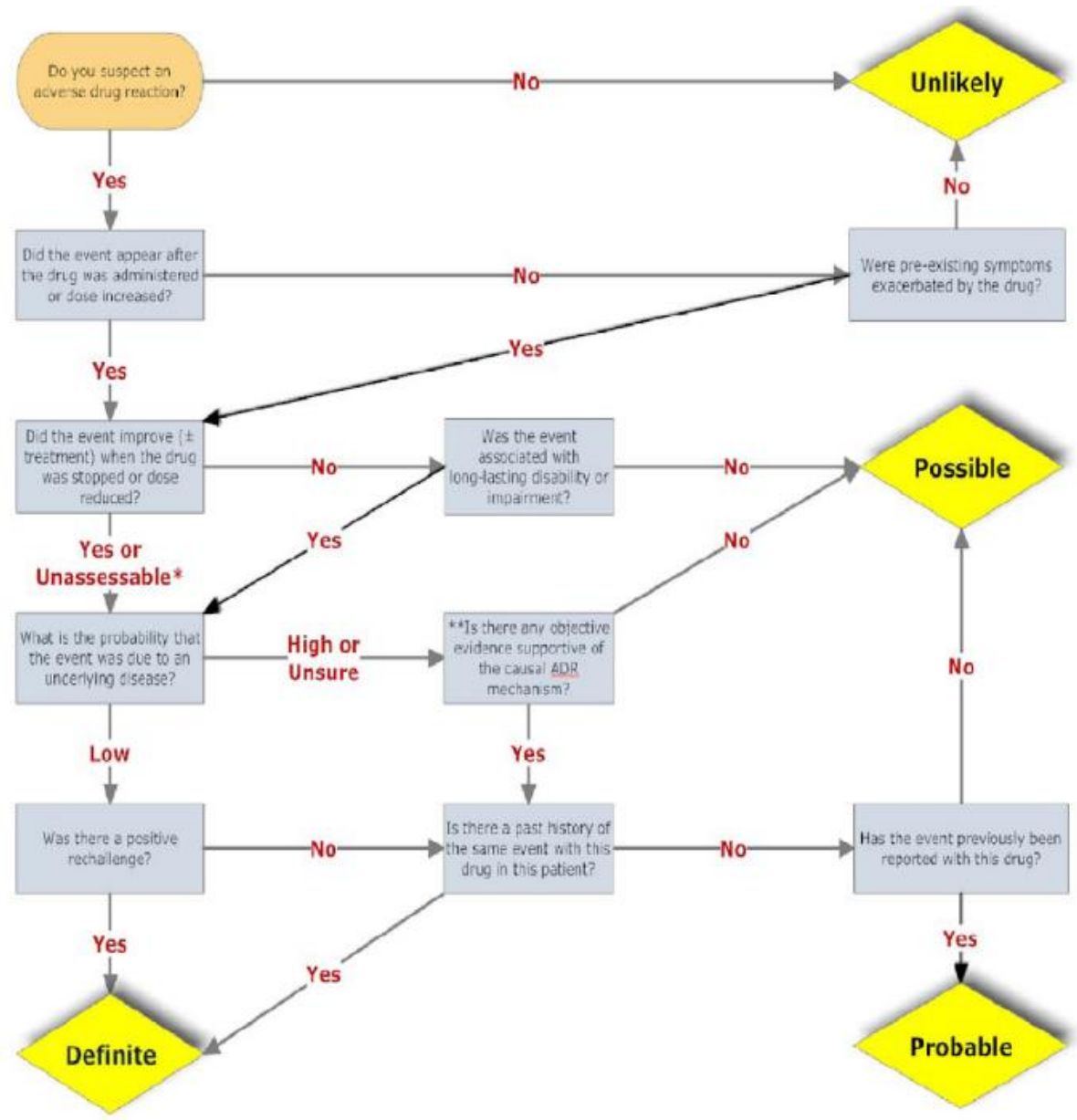
Adverse drug reactions assessment criteria	Yes	No	Not applicable/ unknown
1. Was the timing of AE consistent with an ADR to the suspected drug?	6	−7	0
2. Is the AE a well-documented ADR to the suspected drug?	0	−6	0
3. Are there published reports on this AE that are related to the suspected drug in newborns?	4	−4	0
4. Was the AE likely a change (exacerbation, recurrence, complication, or new manifestation) in a preexisting clinical condition?	−3	7	0
5. Are there any alternative etiologic candidates other than the preexisting condition (eg, concomitant drugs) that are a common cause of the AE?	−3	2	0
6. Was an alternative etiologic candidate confirmed by any objective evidence?	−3	3	0
7. Did the AE improve after suspected drug was discontinued?	4	−1	0
8. Was the AE less severe when the dose was reduced?	4	−2	0
9. Did the AE improve after a specific antagonist was administered?	3	−1	0
10. Did the AE significantly diminish or disappear while patient was still taking the suspected drug?	−2	1	0
11. Did the AE reappear/worsen when suspected drug was reintroduced?	9	−1	0
12. Was the suspected drug detected in blood or other fluids in concentrations known to be toxic?	4	−2	0
13. Is there unequivocal evidence that the amount of the suspected drug received was an overdose for this patient?	4	−4	0
If Total Score ≥ 14 ➔Definite	**Total Score =** _____		
If 7 ≤Total Score ≤ 13 ➔Probable	**Category =** _____		
If 3 ≤Total Score ≤ 6 ➔Possible			
If Total Score ≤ 2 ➔unlikely			

Abbreviations: ADR, adverse drug reaction; AE, adverse event.

Liverpool Adverse Drug Reaction Causality Assessment Tool

The 'Liverpool Adverse Drug Reaction Causality Assessment Tool' (LCAT) was developed as part of the Adverse Drug Reactions in Children (ADRIC) research programme conducted in the North West of England. Whilst conducting the prospective observational studies earlier in the programme, difficulties were faced when trying to use the Naranjo algorithm to assess the paediatric ADR cases. Investigators found that many cases were being classified as unknown despite multiple expert opinions agreeing otherwise. The research team also noted that the justifications for the weighting of each question and the scoring boundaries are not available in any accessible publication. The existing questions in the Naranjo algorithm were reviewed by seven investigators at a consensus meeting and each question retained, removed, modified or combined with another. A new algorithm was created from these decisions and validated through several processes using prospectively collected cases and measuring kappa scores. The resulting product was a flowchart of ten questions which leads the user to a causality assessment of either 'unlikely', 'possible', 'probable' or 'definite'(65). The Liverpool ADR Causality Assessment Tool was produced following difficulties assessing paediatric ADR causality, but was designed to be used to assess ADRs in any age group. When the LCAT was used to evaluate paediatric ADR cases it showed greater inter-rater reliability than the Naranjo method. However, the population observed for ADR cases only included a limited number of neonates, as only surgical inpatient neonates were included in ADRIC. It is not known whether the LCAT will be appropriate for assessing neonatal ADRs. As neonates exhibit different pharmacokinetics and dynamics to those of older children, it is likely that neonates will require population-specific causality assessment methods. However, as there is currently only one known neonate-specific causality assessment method, other options need to be explored. The LCAT was designed to be appropriate for use for assessing paediatric ADRs and so may prove more appropriate for the neonatal population than other tools that have proven difficult to use in children, such as the Naranjo. The decision was made to validate it's use in the neonatal population in this study.

Liverpool Adverse Drug Reaction Causality Assessment Tool



*Unassessable refers to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. Chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressants)

**Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient

Figure 2. Liverpool ADR causality assessment tool.
doi:10.1371/journal.pone.0028096.g002

3.4.2 Assessment process

Summaries of each ADR case were created using information gathered in the 'Suspected Adverse Drug Reaction in a Neonate' proforma. The summaries included the main information regarding the demographics of the neonate, details of the suspected causative drug including dose and timings, a narrative of the reaction itself, the reaction outcome, any significant labour, pregnancy or maternal history and any significant medical history or possible differential diagnoses. Further information from the full case spreadsheet could be requested from the researcher at any time, who could collect additional information from the electronic notes system if necessary.

Copies of the case summaries were given to six assessors, who are detailed in table 5. The assessors were each asked to use the three different causality assessment tools to evaluate the causality of each ADR case. Each assessor was asked to record their assessment of each case using each of the three tools, resulting in three assessments per assessor per case. The process of doing the causality assessments was explained to each assessor either in person or via email. Assessors were given up to one month to complete all assessments. The process of performing the causality assessments was trialled by the two student supervisors prior to the process being undertaken by other assessors.

The assessors were also asked to complete a brief questionnaire regarding the use of each of the three tools after they had completed the assessments, a copy of which can be found in appendix 3. An informal conversation was also had with each assessor upon the completion of the assessments regarding any difficulties and opinions on the task.

Table 5 Details of the six individuals who carried out causality assessments

Assessor	Initials	Designation	Years of neonatal experience
Assessor 1	BP	Consultant neonatologist	10
Assessor 2	BY	Consultant neonatologist	30
Assessor 3	BS	Consultant neonatologist	35
Assessor 4	MT	Consultant neonatologist	25
Assessor 5	DH	Consultant clinical pharmacologist	7
Assessor 6	JM	Specialty registrar (ST6)	5

3.5 Severity assessment

Whilst a neonate-specific method of assessing the severity of ADRs is under development, there are currently no known methods of assessing severity of ADRs in this population that have been validated. However, it was considered important to evaluate the severity of the ADRs that occurred in this study. Therefore a severity assessment of each case was undertaken by the principal investigator using a method outlined in a previous study conducted into ADRs in children in the 1990s(76).

The severity ratings were outlined as follows:

1. Severe: fatal or potentially life-threatening.

2. Moderate: requiring treatment or prolonging stay in hospital.

3. Mild: no treatment required and no effect on length of stay in hospital.

3.6 Statistical analysis

3.6.1 Statistical analysis of ADR cases

Upon completion of the ADR data collection each ADR case was reviewed and data extracted to form collated results. ADR incidence was calculated and expressed as the number of neonates experiencing at least one ADR over the total number of neonates who were inpatients on the unit for at least one day in the nine-week observation period. Other data was represented as frequencies, percentages, ranges, modes and medians. The categorisation of neonates by age and weight used definitions outlined by the EMA in the 'Guideline on the investigation of medicinal products in the term and preterm neonate'(12).

A Fisher's exact test was used to compare the frequency of ADRs by gender occurring on the unit. Sub-group analysis was undertaken using the chi-squared test within the population identified as suffering ADRs. These calculations were performed as part of an exploratory secondary analysis and were not intended to draw conclusions from.

The decision was made to include all observed suspected ADRs in the ADR case analysis. Previous studies have included only those ADRs with the highest causality ratings but it was decided that the validation needed to include all degrees of causality.

3.6.2 Statistical analysis of causality assessments

Upon the completion of all causality assessments by the six assessors the results for each assessor were inputted into a spreadsheet and tabulated for clear presentation. A chi squared test was performed to determine the significance of the number of times each rating was assigned using each tool.

Inter-rater reliability:

Inter-rater reliability was measured by calculating non-weighted and weighted kappa scores. Kappa scores aim to measure the level of agreement between two sets of data above that that would be expected to have occurred by chance alone. Weighted kappas take the amount of difference between pair-wise assessments into consideration e.g. two assessments of definite and probable show better agreement than two assessments of definite and unlikely(77).

Percentage exact agreement and percentage extreme disagreement were also calculated to show the level of concordance between pairs of assessors. Extreme disagreement was defined as a difference of more than one causality interval between the pair-wise assessments e.g. one assessor gives a definite rating where the other gives a possible rating.

A global kappa score was also calculated. This single figure shows the level of agreement between all six assessors for each tool.

Inter-tool reliability:

Inter-tool reliability was also measured by calculating kappa scores to measure agreement between the ratings for the same cases assessed by the same assessor using two different tools. The purpose of this was to analyse whether any two tools produced similar outcomes. This was also measured by calculating non-weighted and weighted kappa scores.

A difficulty was faced when comparing the Karch and Lasagna algorithm to the other two algorithms; the Karch and Lasagna algorithm has five possible outcomes whereas the others have four. Due to the limited amount of research in this field and the need to make a comparison between all tools, a decision was made to adjust for this. Two of the outcome categories in the Karch and Lasagna algorithm were merged to form one outcome. It was decided to merge the categories ‘conditional’ and ‘possible’ as neither of the other two tools contained a ‘conditional’ outcome. This left the tool with four categories: ‘definite’, ‘likely’, ‘possible’ and ‘unlikely’. The likely category was translated to have the same meaning as the ‘probable’ category used in the other two tools.

The level of kappa acceptability for both inter-rater an inter-tool reliability was chosen to be the same as that used in the ADRIC research programme: <0.2=poor, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=good, 0.81-1.00=very good. This was in reference to literature by Altman(65,77).

The following statistical software packages were used for the statistical analyses:

SPSS: IBM® SPSS Statistics®

IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

GraphPad QuickCalc free web calculator: GraphPad QuickCalcs Website

www.graphpad.com/quickcalcs/ Accessed May 2017

3.6.3 Study approval

Sponsorship for this study was obtained from the University of Liverpool on 10th November 2016 after a full committee review, as this project was conducted as part of an MPhil thesis. This approval was for the proposed study outlined in the study protocol found in appendix 1. Appropriate ethical approval was sought through an IRAS application. Ethical approval was granted from the Proportionate Review Sub-Committee of the Wales REC 7 on 7th December 2016, reference number 16/WA/0379. HRA approval was granted on 19th January 2017 and thus sponsorship permission to proceed was provided on 27th January 2017.

3.7 Discussion

Designing this research study took careful planning, and with very few previous studies published, there were limited sources of guidance. Many significant decisions were made regarding the methods of data collection and evaluation for the study. One decision was with regards to who would complete the data collection proforma when an ADR case was suspected. Originally it was planned to make the proformas available to any member of staff to use to report a suspected ADR. However, initial feedback from staff raised concerns that they would not have time to do this or would not know what details to include. From this feedback, the decision was made for the researcher to complete all data collection forms, with staff having the opportunity to use the ADR alert forms. This enabled a consistent data collection process so that the data and detail collected for each ADR case were as similar as possible. This was particularly important for the causality assessment process.

Having the researcher complete the data collection proformas also avoided missing data. However, in a small sample of cases it was difficult to collect all necessary data. In other cases, when the electronic patient notes were searched, it was hard to distinguish between a lack of information because it was omitted accidentally, or omitted because it was considered unimportant. In these situations, questions could be asked to the clinical team, and suspicions monitored before recording an ADR case. Some information will never be recorded, and this is often not a study limitation but an unavoidable matter of life.

Another significant decision was taken with regards to informing parents about the occurrences of ADRs suspected in the study. The Health and Social Care Act 2008 (Regulated Activities) Regulations 2014: Regulation 20 refers to the duty of candour(78). It outlines the

responsibilities of a healthcare provider to be open and honest with relevant service users, and how to communicate in the case of ‘notifiable safety incidents’ occurring. Notifiable safety incidents in this regulation are defined as those causing moderate or severe harm, or causing prolonged pain or psychological harm. Unit practice on the NICU observed in this study is only to disclose those ADRs considered severe to parents of neonates. As disclosing all observed ADRs in this research project would have disrupted unit practice, the decision was made not to inform parents of ADRs detected during this study. Severe ADRs detected by the clinical team would have been discussed with the parents in line with both unit practice and the duty of candour. This was approved by both ethical and sponsorship committees by means of reviewing the proposed study protocol when sponsorship and ethical approval were sought. As the ADRs observed in this study were suspected rather than confirmed, and many received low causality ratings when assessed, it could be considered unethical to disclose unclear information causing unnecessary worry.

Chapter 4: Prospective observation of adverse drug reactions in neonates

To enable the collection of neonatal ADR cases, a prospective observational study was designed, piloted and conducted on the Richard Cooke Neonatal Unit at the Liverpool Women's Hospital. Neonates were observed for nine weeks and continuous reviewing of the neonates' clinical conditions and care over this time, in addition to contributions by staff, resulted in the collection of documented cases of suspected ADRs in neonates. The continuous prospective data collection method meant suspected cases were monitored and documented for several weeks to allow for a detailed documentation of the course of a suspected ADR. A wide range of reactions to many different drugs were suspected to have been suffered by both pre-term and term neonates with a range of medical and surgical conditions. The results below outline the spread of cases that were seen, and demonstrate some of the differences between ADRs recorded prospectively under research conditions and those submitted spontaneously to the MHRA.

4.1 ADRs on the neonatal unit

Over the data collection period, 151 neonates were admitted to the unit (neonates on the transitional care unit were not included in the study). The initial admissions were from the labour and midwife-led units (*55*), operating theatres (*48*) and post-natal ward within the hospital (*36*), and some from other hospitals (*12*). Finally, including the neonates who were already inpatients before the start date of the study (*42*), the total number of neonates studied was 193. In total, 63 reports detailing suspected ADRs were recorded for the study during the data collection period. Of the 63 ADR reports, 56 reports were thought to have arisen from medications prescribed for the neonate, and seven from maternal drugs. No reactions to prescribed paternal medications were observed in this study.

Table 6 gives an overview of the number of ADR reports, the number of neonates involved and the number of reactions and suspected drugs the reports detailed.

Table 6 ADR reports and the number of neonates, reactions and drugs reported

	Number of reports	Number of neonates affected	Number of ADRs detailed on the reports	Number of drugs detailed on the reports
ADR reports detailing prescriptions to neonate only	56	28	68	78
ADR reports detailing maternal prescriptions	7	7	7	11
Total	**63**	**35**	**75**	**89**

4.1.1 Neonate characteristics

35 of the 193 neonates studied on the NICU over the nine weeks experienced an ADR. The incidence of neonates who suffered an ADR was therefore 18.1% (35/193).

Of these 35 neonates, 21 were suspected to have experienced one ADR whilst 14 neonates were suspected to have experienced more than one ADR (Figure 1). The median and mode number of reports per neonate was one. Table 7 outlines the demographics of the neonates experiencing ADRs in this study and the number of reports filed for each subgroup.

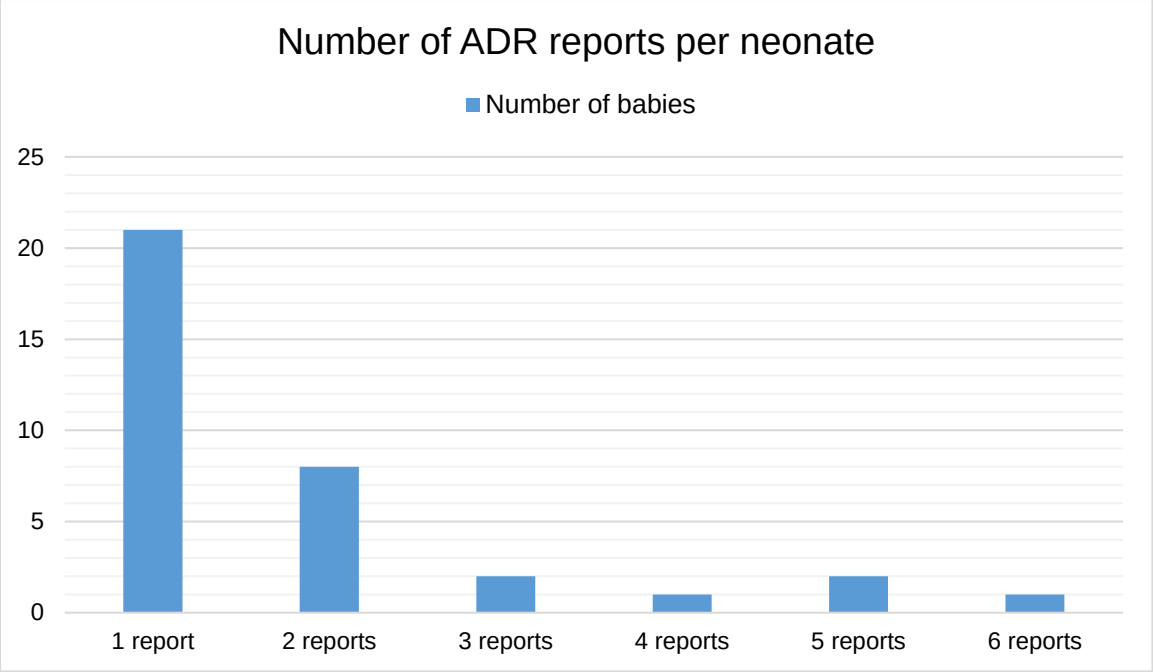


Figure 1 Number of ADR reports per neonate (total number of reports=63)

Table 7 Demographics of neonates experiencing at least one ADR

Neonate characteristics		Number of neonates n=35(%)	Number of suspected ADR reports n=63(%)
Gender	Male	24 (69)	48 (76)
	Female	11 (31)	15 (24)
Gestational age at birth	Extremely preterm (<28 weeks)	12 (34)	33 (52)
	Very preterm (28 to <32 weeks)	5 (14)	8 (13)
	Moderate to late preterm (32 to <37 weeks)	5 (14)	7(11)
	Term neonates (37- 42 weeks)	13 (37)	15 (24)
Birthweight by group	Extremely low birthweight (<1000g)	11 (31)	33 (52)
	Very low birthweight (<1500g)	7 (20)	9 (14)
	Low birthweight (<2500g)	5 (14)	7 (11)
	Normal birthweight (2500g – 4200g)	12 (34)	14 (22)
Corrected gestational age at time of ADR	<28 weeks	5 (14)	11 (18)
	28 to <32 weeks	10 (29)	15 (24)
	32 to <37 weeks	5 (14)	19 (54)
	37 + weeks	15 (43)	18 (29)
Working weight at time of ADR	<1000g	6 (17)	13(21)
	<1500g	9 (26)	20 (32)
	<2500g	8 (23)	15 (24)
	2500g – 4200g	12 (34)	15 (24)
Multiple pregnancy	Singleton pregnancy	33 (94)	59 (94)

Neonate characteristics		**Number of neonates n=35(%)**	**Number of suspected ADR reports n=63(%)**
	Twin pregnancy	2 (6)	4 (6)
	Triplet pregnancy	0 (0)	0 (0)

NB: In four cases, the gestational ages, and thus corrected gestational ages, of the neonates were estimated as the pregnancies were un-booked. Though included in this table, these cases were not included in any further calculations.

In cases where the ADR lasted several weeks and weight changed, the minimum working weight during the ADR period was used for analysis.

The gestational ages of the neonates at birth ranged from 23 + 6 weeks to 40 + 4 weeks. The birth weights of the neonates ranged from 570g to 3990g and the mean birth weight was 1874g. The neonates' corrected gestational ages at time of experiencing an ADR ranged from 26 + 1 weeks to 40 + 5 weeks. The neonates' working weights at time of ADR ranged from 580g to 3990g.

At the time of ADR occurrence, 41 neonates were being cared for in ITU, 15 in HDU, one in the nursery, three in the post-natal wards and three on the delivery unit. In eight cases, the neonate required an escalation of care at the time of the ADR i.e. moving from HDU to ITU.

The number of recorded concomitant drugs prescribed at time of ADR occurrence ranged from 0 to 43, not including resuscitation drugs. The mean number of recorded concomitant drugs prescribed was 13 and the mode was 19. At the time of ADR occurrence, 79% of the neonates in the report were receiving five or more concomitant drugs, and 65% were receiving ten or more.

A Fisher's exact test compared neonates who did not suffer an ADR to those who did, and found there was no significant difference between gender groups (table 8).

Within those neonates who were identified to have suffered an ADR, sub-group analyses were undertaken. Chi squared tests showed there to be significant differences in the number of ADRs experienced by neonates when categorised by gestational age at birth, birthweight, corrected gestational age at time of ADR and working weight at time of ADR. The calculated p-values are displayed in table 8.

The increased number of ADRs seen in the older corrected gestational age category could be explained by sick neonates who were born extremely preterm requiring many medications when they enter this corrected gestational age category as a result of the comorbidities of prematurity.

Table 8 Results of statistical analysis of demographic subgroups

Demographic factor	Statistical test used	Result (p value)
Gender	Fisher's exact	0.1362
Birthweight	Chi squared	0.0047
Corrected gestational age at time of ADR	Chi squared	0.0018
Working weight	Chi squared	0.0101
Gestational age at birth	Chi squared	0.0226

4.1.2 Drugs prescribed on the neonatal unit

The medicines prescribed to all neonates on the unit during the study period, as captured by the BadgerNet electronic patient data system, are shown in table 9.

Table 9 Drugs prescribed to all neonates on the neonatal unit over nine-week period

Drug	Number of neonates prescribed drug over nine-week period
Aciclovir	3
Adrenaline	4
Amiloride	1
Amphotericin	1
Amphotericin- liposomal	2
Aquacel	1
Benzylpenicillin	107
Betamethasone eye drops	2
Caffeine	47
Clotrimazole cream	3
Carobel	1
Cefotaxime	5
Chloral hydrate	2
Chloramphenicol eye drops	1
Chloramphenicol eye ointment	5
Chlorhexidine powder	145
Ciprofloxacin	9
Co-amoxiclav	40
Curosurf (surfactant)	2
Cyclopentolate eye drops 0.5%	2
Dalivit	78
Dexamethasone	4
Dextrose 10%	2
Dobutamine	3
Domperidone	1
Dopamine	5
E45 cream	6
Fentanyl	2
Fluconazole	15
Folic acid	76
Furosemide	13
Gaviscon	2

Drug	Number of neonates prescribed drug over nine-week period
Gentamicin	126
Glycerin suppository	1
Heparinised saline	1
Human normal immunoglobulin	1
Hydrochlorothiazide	10
Hydrocortisone	8
Hypromellose eye drops	5
Ibuprofen	5
Immunoglobulin	2
Insulin	2
Linezolid	2
Liothyronine sodium	1
Magnesium glycerophosphate	1
Meropenem	1
Metronidazole	11
Midazolam	5
IV morphine	1
Oral morphine	4
Morphine sulphate	4
Multivitamins	2
Nitric oxide	5
Nystatin suspension	32
Ofloxacin eye drops	1
Omeprazole	1
Orobase	5
Paracetamol	14
Phenobarbital	2
Phosphate	20
Promethazine	2
Propranolol	1
Prostaglandin E2	2
Ranitidine	7
Sildenafil	1

Drug	Number of neonates prescribed drug over nine-week period
Sodium bicarbonate	2
Sodium chloride	18
Sodium feredetate	23
Spironolactone	13
Suxamethonium	1
Teicoplanin	9
Total Parenteral Nutrition	44
Vancomycin	1
Vecuronium	2
Vitamin K	20
Total	**1009**

4.1.3 ADR report characteristics

75 different ADRs were suspected on 63 reports. The number of suspected ADRs exceeds the number of reports as some reports detailed two different reactions to the same drug(s). In these cases, reactions were grouped together e.g. both flat affect and respiratory depression caused by morphine.

Reports of suspected ADRs to neonatal medications

Table 10 details the reported reactions to drugs prescribed directly to the neonate (i.e. the 56 of the 63 reports that do not detail reactions to maternal medications).

Table 10 Clinical presentations of the observed ADRs and the drugs suspected to have caused them

Clinical Presentation	**Total number of neonatal ADRs reported in study**	**Drugs suspected to cause this reaction**
General disorders + administration site disorders:	***6***	
Pyrexia	4	Aciclovir, prostaglandin E2
Decreased weight gain	1	Dexamethasone
Extravasation reaction	1	Dextrose 10% solution with sodium and potassium, aciclovir
Blood and lymphatic system disorders:	***7***	
Thrombocytopenia	3	Gentamicin, benzylpenicillin, linezolid
Thrombocytopenia + leucopenia	2	Benzylpenicillin
Arterial thrombus	1	Immunoglobulins
Neutropenia	1	Hydrochlorothiazide, spironolactone
Cardiovascular disorders:	***8***	
Tachycardia	4	Dopamine, dobutamine, cyclopentolate eye drops, phenylephrine eye drops, hydrocortisone
Hypertension	2	Dopamine, hydrocortisone
Bradycardia	1	Propranolol
Heart block	1	Digoxin
Cardiopulmonary disorders:	***4***	
Apnoeas + desaturations + bradycardia	1	Prostaglandin E2
Desaturations + bradycardia	1	Cyclopentolate eye drops, phenylephrine eye drops

Clinical Presentation	**Total number of neonatal ADRs reported in study**	**Drugs suspected to cause this reaction**
Hypertension leading to pulmonary haemorrhage	1	Dopamine
Hypertension + large urine output	1	Dopamine, dobutamine
Respiratory disorders:	***2***	
Apnoea + desaturations + raised CRP	1	Bexsero (meningococcal) immunisation
Apnoea	1	Cyclopentolate eye drops, phenylephrine eye drops
Gastrointestinal disorders:	***7***	
Constipation	2	Sodium feredetate
Watery stoma losses	2	Co-amoxiclav, gentamicin
Bloody GI aspirates	1	Hydrocortisone
Diarrhoea	1	Aciclovir, ciprofloxacin, teicoplanin
Vomiting	1	Cyclopentolate eye drops, phenylephrine eye drops
Hepatobiliary disorders	***0***	
Renal and urinary disorders:	***6***	
Renal failure/kidney injury	3	Gentamicin, benzylpenicillin
Urinary retention	2	Midazolam, phenobarbital
Reduced urine output	1	Vecuronium, midazolam
Nervous system disorders:	***6***	
Flat affect	3	Morphine
Cerebral haemorrhage	1	Dobutamine
Respiratory depression	1	Morphine
Respiratory depression + flat affect	1	Morphine
Metabolic disorders:	***8***	
Electrolyte disturbance	2	Furosemide, amiloride
Hypernatraemia	2	Sodium supplements

Clinical Presentation	**Total number of neonatal ADRs reported in study**	**Drugs suspected to cause this reaction**
Hyponatraemia	2	Hydrochlorothiazide, spironolactone
Hyperglycaemia	1	Hydrocortisone
Metabolic acidosis	1	Heparinised saline, sodium chloride
Dermatological disorders:	***0***	
Investigation results:	***2***	
Deranged electrolytes, high creatinine, low calcium	1	Gentamicin
Raised creatinine	1	Furosemide

The 56 reports for suspected neonatal ADRs (63 total ADRs minus the seven suspected to be due to maternal medications) detailed a total of 78 prescriptions. Overall 31 different drugs were suspected to have caused neonatal ADRs. 36 ADRs were reported to be caused by one drug, 18 were reported to be caused by two drugs and two were reported to be caused by three drugs.

Gentamicin was suspected to have caused the most ADRs (*8*), with morphine (*6*) and dopamine (*5*) being the next most common.

The most common drug groups (by ATC classification) causing ADRs were those drugs in the cardiovascular system group (*28*), the anti-infectives for systemic use group (*22*) and the nervous system group (*9*). Details of the reactions suspected to have been caused by drugs in these groups can be found in table 11.

Thirty ADR reports suspected one or more drugs that had been prescribed to the neonate off-label. Table 12 lists these drugs and the number of ADRs reports that detailed them as suspected drugs.

Table 11 Drug groups (by ATC classification) and ADRs suspected to have been caused

Drugs (by ATC classification)	ATC code	Number of times reported	Number of neonates
Alimentary tract and metabolism	**A**	**3**	**3**
Mineral substitutes	*A12*	*3*	3
Anti-infectives for systemic use	**J**	**22**	**13**
Anti-bacterials for systemic use	J01	17	9
Anti-virals for systemic use	J05	3	2
Immune sera and immunoglobulins	J06	1	1
Vaccines	J07	1	1
Blood and blood-forming organs	**B**	**4**	**4**
Antithrombotic agents	B01	1	1
Anti-anaemic preparations	B03	2	2
Blood substitutes and perfusion solutions	B05	1	1
Cardiovascular system	**C**	**28**	**15**
Cardiac therapy	*C01*	*14*	7
Diuretics	*C03*	*10*	5
Vasoprotectives	*C05*	*3*	2
Beta-blocking agents	*C07*	*1*	1
Musculoskeletal system	**M**	**2**	**2**
Muscle relaxants	M03	2	2
Nervous system	**N**	**9**	**9**
Nervous system-analgesics	*N02*	*5*	5
Nervous system-antiepileptics	*N03*	*1*	1

Drugs (by ATC classification)	**ATC code**	**Number of times reported**	**Number of neonates**
Psycholeptics	*N05*	*3*	3
Sensory organs	**S**	**8**	**3**
Ophthalmologicals	S01	8	3
Systemic hormonal preparations	**H**	**2**	**2**
Corticosteroids for systemic use	H02	2 (64)	2

Table 12 Drugs prescribed to the neonate off-label

Name of drug prescribed off-label	Number of ADR reports
Amiloride	1
Cyclopentolate eye drops	4
Dexamethasone	1
Dopamine	5
Furosemide	3
Immunoglobulins	1
Hydrochlorothiazide	3
Hydrocortisone	4
Linezolid	1
Morphine	5
Phenobarbitone	1
Sodium chloride	1
Spironolactone	3
Vecuronium	2

The ADRs to drugs prescribed to the neonate were evaluated through a severity assessment. A neonate-specific method of assessing severity of ADRs is still under development, so in this study a method which has previously been used to evaluate paediatric ADRs was used(76). The severity ratings given to each ADR report can be found in table 13. Of the 56 ADRs to neonatal prescriptions, 28 were classified as being mild ADRs, i.e. they did not require treatment or prolong the neonate's stay in hospital and the remaining 28 were classified as moderate ADRs, i.e. they did require treatment or lengthen the neonate's stay. No ADRs were classified as severe, i.e. being fatal or potentially life-threatening. It is possible that a neonate-specific method of assessing severity may yield different results.

Table 13 All ADRs observed and the given severity ratings

ADR	Severity rating
Hydrocortisone and hyperglycaemia	Moderate
Morphine and flat affect	Mild
Hydrochlorothiazide/spironolactone and hyponatraemia	Moderate
Hydrochlorothiazide/spironolactone and hyponatraemia	Mild
Furosemide and electrolyte disturbance	Moderate
Furosemide/amiloride and electrolyte disturbance	Moderate
Hydrocortisone and bloody GI aspirates	Moderate
Oral morphine and flat affect	Moderate
Furosemide and raised creatinine	Moderate
Gentamicin and AKI	Moderate
Co-amoxiclav/gentamicin and watery stoma losses	Mild
Digoxin and heart block	Moderate
Dexamethasone and decreased weight gain	Mild
Propranolol and bradycardia	Moderate
Sodium supplements and hypernatraemia	Moderate
Sodium feredetate and constipation	Mild
Dopamine and tachycardia	Moderate
Inotropes/hydrocortisone and high BP/pulmonary haemorrhage	Moderate
Gentamicin and acute renal failure	Moderate
Hydrochlorothiazide/spironolactone and neutropenia	Mild
Morphine and respiratory depression	Moderate
Sodium feredetate and constipation	Mild
Sodium supplements and hypernatraemia	Mild
Dextrose and extravasation reaction	Mild
Aciclovir and pyrexia	Moderate
Prostaglandin E2 and pyrexia	Mild
Gentamicin/benzylpenicillin and thrombocytopenia	Mild
Gentamicin and deranged electrolytes, high creatinine, low calcium	Mild
Gentamicin and thrombocytopenia	Mild
Phenylephrine/cyclopentolate eye drops and tachycardia	Mild
Meningococcal vaccine and apnoea, desaturations, raised CRP	Moderate
Phenylephrine/cyclopentolate eye drops and apnoea	Moderate
Phenylephrine/cyclopentolate eye drops and vomit	Mild

ADR	Severity rating
Midazolam and urinary retention	Mild
Sodium chloride and metabolic acidosis	Moderate
Vecuronium and urinary retention	Moderate
Linezolid and thrombocytopenia	Moderate
Phenylephrine/cyclopentolate eye drops and bradycardia	Moderate
Benzylpenicillin and thrombocytopenia and leucopenia	Mild
Prostaglandin E2 and pyrexia	Mild
Prostaglandin E2 and apnoea, desaturations and bradycardia	Mild
Immunoglobulins and arterial thrombus	Moderate
Vecuronium/midazolam and reduced urine output	Moderate
Morphine and respiratory depression and flat affect	Moderate
Benzylpenicillin and thrombocytopenia and leucopenia	Mild
Morphine and flat affect	Mild
Inotropes and tachycardia	Mild
Dobutamine and cerebral haemorrhage	Mild
Inotropes and hypertension and large urine output	Mild
Gentamicin and renal impairment	Moderate
Dopamine and hypertension	Moderate
Antibiotics and diarrhoea	Mild
Co-amoxiclav/gentamicin and watery stoma losses	Mild
Hydrocortisone and hypertension	Mild
Prostaglandin E2 and pyrexia	Mild
Vecuronium and tachycardia	Mild

The suspected drug was continued in 14 cases. The dose of the suspected drug was changed in 10 cases. The suspected drug was stopped in 34 cases. In 12 of these cases the drug was stopped due to the ADR and was only substituted with an alternative drug in two of the twelve cases.

Of the 34 cases where the drug was stopped, 30 cases had a documented outcome of 'improvement of clinical symptoms/observations/investigations'. Of the 14 cases where the drug was continued, six had this same documented outcome, seven 'no change of clinical symptoms/observations/investigations' and one 'deterioration of clinical symptoms/observations/investigations'.

15 reports included details of treatment given due to the clinical sign that may have been caused by an ADR. Examples included hyponatraemia being treated with sodium supplements, platelets given in the case of thrombocytopenia and mechanical ventilation following respiratory depression.

4.1.4 Suspected ADRs to maternal medication

Of the 63 suspected ADRs, seven of these were suspected to be due to maternal medications. Two were due to opiates prescribed in labour, and the remaining five were due to medications taken during pregnancy.

4.1.5 Reporter characteristics

All ADR cases were reported by the researcher, but of these 16 were prompted by other ward staff (table 14). The ADR alert forms were used to report two cases, one by a nurse and one by a senior house officer (SHO).

Table 14 Number of alerts to ADRs by different members of clinical team

Designation	Number of alerts to ADRs
Consultant	7
Registrar	1
SHO	6
Nurse	2
Pharmacist	0
Other healthcare professional	0

4.2 Comparison to Yellow Card reports

A recently published paper described all the Yellow Card reports detailing neonatal ADRs submitted to the MHRA between the years 2001 and 2010 in the UK(6). It was possible to compare the ADRs observed in this prospective observational study to those reported to the MHRA in the studied ten-year period.

The most noticeable difference was the overall number of reports. The MHRA received 97 neonatal ADR reports in the ten-year period, and 56 neonatal ADR reports were collected in the nine-week study period alone.

Both sets of results report more ADRs occurring in males. It was not possible to compare the ages and weights of the neonates experiencing ADRs as the Yellow Card reports were missing some of this significant data. Whilst the paper establishes that the neonates were correctly identified as neonates by being less than 28 days old, it reports that only 23 of the Yellow Card reports gave an exact gestational age at birth.

The most commonly reported drug in the 97 Yellow Cards was the swine flu vaccination *(8)* and a further three reports related to the DTPw HIB vaccination. This prospective observational study reported only one ADR to a vaccination. However, there was no known epidemic of swine flu during the study period and only a few neonates were inpatients when they reached the appropriate age for first immunisations to be given. This study reported the most reactions to gentamicin *(8),* morphine *(6)* and dopamine *(5).*

The most commonly reported reactions on Yellow Card reports were dermatological reactions, yet ADRIN only observed one reaction of this kind, an extravasation reaction. Six Yellow Card reports detailed reactions causing bradycardia yet only one case of this was observed in this study. The study reported mainly cardiovascular and metabolic reactions (8 each) with single reaction types receiving the most reports being tachycardia and pyrexia (4 reports each).

In its results and discussion, the paper details those drugs that received no Yellow Card reports despite having well documented safety warnings. These were codeine, ceftriaxone and Kaletra. This study did not observe any suspected reactions to these drugs which are not used on this neonatal unit. The paper also comments on the absence of any reports for surfactant and this study also did not observe any ADRs to surfactant. When the electronic patient notes system (BadgerNet) generated a report of all medicines prescribed to all neonates over the nine-week study period (table 9), only two neonates were reported to have received surfactant. This appears to be an underestimation, as although many more neonates will have received surfactant during this time, this drug is usually administered in the first few moments of life when the neonate is on the labour ward, and so therefore this drug will not be

recorded by BadgerNet as a drug prescribed on the neonatal unit. Drugs prescribed to the neonate before admission to the NNU were excluded in this study, so this may go some way to explain the absence of any ADR reports for surfactant in this study. However, as the BNFc does contain safety warnings for surfactant, it would be thought that some Yellow Card reports may have been filed in the 10 years studied in the comparison paper(6).

Lastly the paper comments on a seemingly underreported number of ADRs to antibiotics, only ten, despite antibiotics being commonly used in neonatal care. This study observed 12 reports of neonatal ADRs to 17 antibiotic prescriptions, 22% of all suspected drugs.

Table 15 Comparison of neonatal Yellow Card reports submitted to the MHRA between 2001 and 2010 and reports collected in the ADRIN study

Factor	Yellow Card reports	ADRIN study
Frequency of reports	97 in 10 years	63 in 9 weeks
Gender of neonates		
Males	52 (53.6%)	48 (76.2%)
Females	42 (43.3%)	15 (23.8%)
Unrecorded	3	0
Most common reactions	Rashes- 14 Erythema- 7 Bradycardia- 6	Tachycardia- 4 Pyrexia- 4 Flat affect- 3
Most common drugs	Swine flu vaccine- 8 Caffeine- 5	Gentamicin- 8 Morphine- 6 Dopamine- 5

4.3 Discussion

Following on from the large-scale study into adverse drug reactions in children (ADRIC), this study has begun to contribute to the dataset involving ADRs in neonates. It took place in a tertiary neonatal unit treating both term and preterm neonates. The unit manages a wide range of medical and surgical conditions, including referred complex cases, many requiring multiple medications. For the neonatal population, this study is the first to compare three causality assessment methods that have been used to examine the extent to which a medicine can be ascribed to an adverse drug reaction.

4.3.1 Incidence and frequency of reactions

This study observed 63 reports of neonatal ADRs over a nine-week period, 56 of which were thought to be due to prescriptions for the neonate, and the remaining seven from medications used by the mother. Due to the limited resources and time, it was not possible to record data about neonates who were not reported to have experienced an ADR. Of the 193 neonates that were observed over the nine-week period, 35 were suspected to have experienced at least one ADR, an incidence of 18.1%. This is in keeping with a recent observational study into ADRs in neonates(46). However, there were factors which could have reduced the accuracy of this estimate, such as the method of ADR detection. As well as this, all observed ADRs are included in this calculation whereas previous studies have only included ADRs with the highest causality ratings in incidence calculations. Due to the difficulties in performing reliable causality assessments, some of which this study has demonstrated, a crude incidence rate was calculated.

Previous studies have estimated ADRs to cause 0.2% of neonatal admissions(44). In this study, seven neonates were admitted from the delivery suite or post-natal ward with suspected ADRs, and six of these were suspected ADRs to maternal drugs. The incidence of ADRs causing admission has been estimated to be much higher in children, but several factors mean that neonates are much less likely to be admitted due to an ADR. Neonates, by WHO definition, only have 28 days to be classed as a neonate admitted with an ADR. Preterm neonates will have longer, but by being born preterm they will most definitely be admitted to neonatal care anyway. The majority of neonates in NICUs are those born preterm or suffering congenital defects or complications from labour and/or delivery. The dilution effect of these neonates masks those neonates who are admitted due to an ADR. A neonate discharged home well after birth is unlikely to need any medicines, and in this study any sick neonates admitted from home will have been admitted to the local children's hospital, not the NICU studied. Additional research into ADRs causing neonates to be admitted from home, or those occurring in the community, may yield different results to the ADRIN study.

As sick neonates make up a relatively small proportion of the total number of inpatient children in the UK, a much larger scale study is needed to assess ADRs in neonates and to be able to give a valid estimate of incidence. The ADRIC programme was undertaken by a team of researchers at one of the largest children's hospitals in the UK over a one-year period. One of the only prospective studies into neonatal ADRs to date also collected data over a one-year period, in which time 322 neonates were observed. Neonatal units are normally small such that an optimally designed study should be multi-centric. This opportunity was explored with ADRIN as another tertiary neonatal unit is located less than 20 miles away from LWH. The decision was made not to pursue this as it was thought that time and resources were better spent collecting reliable, accurate data from one site. The collection of ADR reports was undertaken by a single researcher, and whilst it would have been possible for additional people to do this in other sites, it would be difficult to regulate this to avoid bias. The addition of a researcher without any other clinical commitments would be necessary, as well as an identical introduction of the study to the second unit. ADRIC used a team of researchers trained in ADR data collection at one site who could communicate with each another if they faced any difficulties. There is most likely not a neonatal unit in the world large enough to conduct the same scale study at one site, but multiple researchers working at a unit each could be trained together and communicate processes and findings regularly.

This study used the definition of an ADR defined by Allegaert(10). This definition allows for the inclusion of ADRs to drugs that have been prescribed unlicensed or off-label, a practice which commonly occurs in neonates. Had other definitions of ADRs been used for this study the frequencies of ADR reports seen may have been different.

Many of the ADRs reported in this study would not have been included under Laurence's definition. 'A drug at doses intended for therapeutic effect (or prophylaxis or diagnosis)' may not have allowed for the ADRs reported detailing off-label prescriptions in this study (30/63 reports). A 'harmful or significantly unpleasant effect' would rule out those cases reported in this study that could be considered milder ADRs, even though many still affected the care of the neonate. Furthermore, it is impossible to tell which ADRs cause a 'significantly unpleasant effect' when the affected neonate cannot communicate symptoms to a clinician. What might seem to be a minor and/or easily treated reaction could be silently causing significant distress to the neonate e.g. urinary retention. Prediction of hazard from future use is also difficult to assess in a population where re-challenges are infrequent, and any future use may occur when the neonate is older and thus physiologically different(8). The same argument stands for Edwards and Aronson's definition(9).

4.3.2 Types of reactions

This prospective observational study observed a wide range of reaction types and there was at least one ADR report for nearly every organ system. It was noted that no hepatobiliary effects were reported. Some such ADRs may have been missed, as ADRs such as jaundice relating to TPN use are well documented. However, as is the case with many other investigations in neonates, changes in liver function tests are difficult to attribute to iatrogenic cause as they are commonly associated with other clinical conditions such as infection. The only reported ADR to affect the skin was an extravasation burn. On the NICU, drips used to administer IV medications to neonates are monitored very closely and any drug known to be an irritant to veins and skin is often administered through a long line. Another reason for this could be that many dermatological ADRs are immune-mediated and preterm neonates lack the immune exposure to build up the potential cross reactions.

Although the most commonly reported ADRs types were in the cardiovascular and metabolic disorders categories, a larger scale study is needed to determine the full spread of neonatal ADR types. There are unique difficulties in observing some reactions in neonates. For example, it is difficult to detect some respiratory effects in neonates who are ventilated, as the neonates were in 36 of the 63 suspected ADR reports in this study. Gastrointestinal effects may become less apparent in neonates who are temporarily nil by mouth and skin changes can be difficult to distinguish from the very delicate and thin skin of a preterm neonate. As neonates cannot communicate, work is needed to define the physiological parameters in which neonatal norms lie, and further research is being conducted in this field.

When the ADRs in this study were assessed for severity, 28 ADRs were assessed as being mild and 28 were assessed as being moderate. No ADRs were assessed as being severe. However, the severity assessment method used was not neonate-specific, and it is clear that the severity categories may be difficult to apply to this population. For example, this method of severity assessment refers to prolongation of patient stay. However, many sick preterm neonates will be inpatients for several months, so it will be difficult to assess whether an ADR truly prolonged an already lengthy stay. Additionally, some ADRs in neonates may not be treatable, but this does not necessarily mean they are not severe. Finally, in some neonates, it will be hard to assess whether an ADR is potentially life-threatening when being born very preterm in itself is extremely high risk. It is likely that using a neonate-specific method of assessing severity may yield significantly different results and find some of the collected cases as severe.

Absence of communication by neonates makes it difficult to detect an ADR, but also to determine the pathophysiology. This study observed four reports of ADRs to eye drops used

for retinopathy of prematurity screening, cyclopentolate and phenylephrine eye drops. However, these eye drops are known to cause stinging in the eye, so it is impossible to know whether the effects observed were due to the drug itself, or the pain they caused. Whilst eye drops causing pain is ultimately still an ADR, it is difficult to suggest a solution when the full pathophysiology is unknown. The use of these drops in older children or adults must have first lead to the discovery that they cause pain, but the reaction profile in neonates could be different.

The NICU studied in ADRIN was a tertiary unit treating extremely preterm and sick neonates. It would be interesting to compare the reactions suspected and reported in this study to those observed in secondary and primary units, those in the community and those in surgical units. These settings, whilst they all treat sick neonates, will use a different array of drugs in different proportions. The unit studied in ADRIN does not care for neonates receiving general anaesthetic as a surgical unit would. Neonates treated in the community are less likely to be suffering from additional comorbidities which would veil the diagnosis of an ADR. A separate study monitoring neonatal adverse drug reactions to drugs given in the community could be carried out.

Further research could be done to follow up those neonates who do experience ADRs to observe the long-term effects. For example, oxygen is known to be linked to the development of retinopathy of prematurity in preterm neonates, but historically the effects were not observed until the neonate was older.

4.3.3 Types of drugs

The most common drug categories reported in this study were cardiovascular system drugs, anti-infectives for systemic use, nervous system drugs and sensory organ drugs. The data collection period in this study was too short to determine whether there was a predominance of ADRs in any drug categories, but larger scale studies may demonstrate if this is the case. It is difficult to determine whether certain drug types cause more ADRs because they are the most harmful or because they are more commonly prescribed, or indeed, a combination of both.

It was interesting to note that there were no ADRs to surfactant observed in ADRIN. The ADRIN team were aware that no ADRs to surfactant were submitted via the Yellow Card Scheme between 2001 and 2010, and so were alert to cases of these ADRs(6). Despite this, none were observed. As surfactant is administered in the first few minutes of a neonate's life, it is usually prescribed and documented before the neonate reaches the neonatal unit, and thus may not be suspected in ADRs that occur in the first few days of life. As shown in table 9, there were only two neonates who received surfactant on the neonatal unit over the nine-

week period. Experiments into the significance of surfactant in neonatal lung function and development first began in the late 1920s(79). For the past 25 years, surfactant has been an essential and commonly used drug in neonatal care and it is likely that these years of reviewed use has led to a safe drug(79). Although ADRs to surfactant have occurred in neonates in the past, it is likely that a larger study would be needed to detect these ADRs(49).

A recent quasi-systematic review outlined the most commonly prescribed drugs in NICUs worldwide(24). It found nine of the top twenty most cited drugs were also listed on the A-PINCH list, a list of medications that pose high risks if medication errors occur(80). The list includes anti-infectives, potassium and concentrated electrolytes, insulin and narcotics and sedatives, all of which are used on neonatal units. The other two groups, chemotherapy agents, and heparin and other anticoagulants, are not routinely used on neonatal units. Gentamicin and morphine, the most commonly reported drugs in this study, also appear on the A-PINCH list, and in total 22 of the 78 reported drugs in this study are A-PINCH listed drugs(24)(80). Worryingly, given that anti-infectives feature on the A-PINCH list, there were only ten UK Yellow Card reports detailing neonatal ADRs to antibiotics between 2001 and 2010(6).

The four ADRs to cyclopentolate and phenylephrine eye drops demonstrate that drugs used to support diagnostic procedures can cause ADRs, even those used for a common procedure in neonates. However, these ADRs could be considered minor and a short-lived price worth paying for better outcomes for the future eye sight of affected neonates. This demonstrates how reporting ADRs could have the ability to affect routine neonatal care, not just those drugs used for the sickest neonates.

4.3.4 Risk factors

There was insufficient data collected in this prospective study to carry out the statistical analysis necessary to comment on potential risk factors. Neonates represent a unique population in relation to risk factors. As the majority of neonates needing neonatal care input are born preterm, it may be hard to distinguish neonatal risk factors for developing an ADR from the risk factors for preterm birth. Previous literature has shown the number of medications and the percentage of unlicensed/off-label medications to be significantly associated with increased risk of an ADR(76). In ADRIN, 65% of the suspected ADR cases occurred in neonates who received 10 or more medications at the time the ADR was suspected to have occurred. It has been theorised elsewhere that ADRs to off-label or unlicensed drugs risk being unreported(81).

4.3.5 Reporting and underreporting

This study observed a considerable number of ADR reports in a short data collection period. Though there are varied definitions, methodologies and guidance in neonatal pharmacovigilance, most research agrees that a considerable rate of underreporting is currently occurring.

It is highly likely that underreporting also occurred in this study. The limited resources for the study meant it was impossible to monitor every neonate on the unit for possible ADRs 24 hours a day, seven days a week. It is likely that the results of this study would have varied had the researcher been a clinician. This could be interpreted in different ways; that a more experienced clinician would detect more ADRs, they would better understand the pathologies mimicking them, or an experienced clinician would have been less sensitive to ADRs because many clinicians consider anticipated side effects not to be ADRs [Arnott, personal communication, unpublished results from ADRIC].

It is difficult to measure the effectiveness of an ADR detection strategy without knowing the true number of ADRs that have occurred. In this study, one extravasation injury was detected and reported. BadgerNet, the electronic patient notes system, can generate a report of the number of extravasation injuries that have been documented in all patients' notes in a given time period. Staff are also asked to complete an 'adverse clinical event' form for extravasation injuries. As one possible way of measuring the effectiveness of the ADR detection methods in this study, these three sources of information were compared. BadgerNet also only reported one extravasation injury in the nine-week study period, however this was a different extravasation injury to the one reported in the study. There were no adverse clinical event forms completed in the nine-week period. This suggests that the ADR detection and reporting intervention in ADRIN could be more effective than relying of staff reporting alone.

However, even though the ADR detection and reporting intervention was effective in collecting cases of suspected ADRs in this study, it relied on an independent researcher. The reporting technique may need to be adjusted if it were to be implemented into clinical practice and undertaken by staff with other clinical duties. One consideration is the data collection proforma. As the researcher completed this in the study, the data collection process was consistent and omissions in detail were infrequent. However, the proforma may need to be adapted for it to be completed by staff in routine clinical practice. Some fields may need to be made more specific to collect the level of detail required for a causality assessment to be undertaken. Another possible adaptation could be to create an electronic copy of the ADR case reporting form which could be used alongside the electronic patient notes system. Certain fields could be automatically completed using data extracted from BadgerNet, which would save staff time.

A more sophisticated database that could do this was used successfully in the ADRIC programme. This concept could also work in reverse, prompting clinical staff to document details that may be relevant to an ADR when writing patient clinical notes. This would help alleviate some of the difficulties faced when it is not known whether certain details are not recorded because of human error, or because they were considered unimportant. For example, if a neonate were to be prescribed prostaglandin, prompts to comment on the neonate's temperature could alert staff to an ADR and help with future data collection if an ADR were to occur. An electronic database could also help monitor neonates that do not experience an ADR. If data could automatically be collected on every neonate admitted to the unit over a given study period, some commentary may be able to be made regarding possible risk factors for developing an ADR.

Of the 63 ADR reports collected, only 16 of these were prompted by members of staff other than the researcher. This was despite multiple efforts to ensure every member of staff was encouraged to report all ADRs throughout the data collection period and beyond. Doctors, and specifically consultants, reported the most suspected ADRs to the researcher whereas only two reports were prompted by nurses. However, more time was spent with the doctors on the unit through handovers and ward rounds and there are many more nursing staff who regularly change shifts. It was disappointing that no reports were prompted by pharmacists despite an introduction of the study to them, but further interventions to include pharmacists in the data collection may have prompted different results. Having a clinical pharmacist regularly present to consult with during the study would have enabled the researcher to query any ADRs, as well as helping alert the researcher to any further ADRs. ADRIC found that using clinical pharmacists was an effective way of collecting paediatric ADR cases. There is a strong argument for clinical pharmacists being the most appropriate staff members to monitor ADRs, either as independent researchers or as part of routine clinical practice, given the nature of their work and knowledge with regards to the safety of medicines. Had the data collection period been extended, it would have been interesting to observe whether additional, more varied educational and motivational interventions would have boosted the number of ADRs reported.

Pharmacovigilance is defined by WHO as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'(43). This study addressed the detection and assessment of ADRs. Whilst the study demonstrated some methods that could be used for ADR detection, it also outlined some of the flaws with these methods and identified that more work is needed to make detection and assessment of ADRs a routine part of neonatal care. The addition of a standalone researcher

to collect reports of suspected ADRs resulted in the detection of a considerable number of ADRs, but it is not feasible to employ someone for this purpose alone.

Whilst this study is one of the only existing studies detailing prospective observation of neonatal ADRs, more work exists detailing how ADR detection and reporting in children could be improved. In the late 1990s, establishing a Paediatric Regional Monitoring Centre was piloted to observe whether this intervention would stimulate ADR reporting. A significant increase in paediatric ADR reporting resulted, increasing the number of paediatric Yellow Card reports as a percentage of total Yellow Card reports for the region above the national average. However, still only one report of an ADR in a neonate was received using this approach (81). Other proposed methods for improving pharmacovigilance in neonates, some of which have been successful in adults, include computerised systems, studies into individual ADR signals, epidemiological approaches, pharmacogenomic approaches and increased involvement of families(11).

Understanding and prevention of ADRs was not addressed in ADRIN, but the cases collected could be further assessed in future research to contribute to these aspects of pharmacovigilance.

4.3.6 Comparison of results to Yellow Card reports to the MHRA

The MHRA guidance on reporting paediatric ADRs changed recently to encourage the reporting of only those ADRs considered to be serious or result in harm. However this guidance was only published in September 2014 meaning the ADRs reported between 2001 and 2010 should have been in line with the previous guidance to report all ADRs in children(13). The different rates of reporting of ADRs to neonatal medicines were 0.187 reports/week and 6.22 reports/week for the Yellow Card Scheme and the ADRIN study respectively. The active surveillance performed in the study resulted in 33 times as many reports as routine submission to the MHRA.

The Yellow Card reports detailed 11 reports of ADRs to vaccinations, yet the most commonly reported drugs in this study were gentamicin, morphine and dopamine. Vaccines receive a large amount of both positive and negative media attention and are often the subject of large public health campaigns. Media attention to publications such as the reprimanded MMR and autism hypothesis paper have not helped in encouraging parents to vaccinate their children(82). Many people feel concern over being given doses of pathological organisms, even though many vaccines are not live, such that high anxiety regarding their use makes patients more aware of side-effects and more likely to report them. Receiving a vaccination is stressful for both the child and the onlooking parent. These factors sensitise parents, patients and healthcare practitioners to the side-effects of vaccinations. However, even though

vaccinations received the highest number of Yellow Card reports, the number is low in comparison to the number of vaccines that would have been administered to neonates over the 10-year period.

All suspected ADRs regardless of perceived severity and causality were reported in this prospective observational study. As anyone can report a suspected ADR to the Yellow Card Scheme, the 97 Yellow Card reports included reports of ADRs suffered by neonates in the community and reports by parents. The study only observed neonatal ADRs occurring in an inpatient setting and reporting by parents was not included. The ADRIC research programme conducted a qualitative study into the opinions of parents regarding reporting ADRs through the Yellow Card Scheme. A wide range of opinions were apparent, including the assumption that the task of ADR reporting needs to be carried out by professionals rather than parents. Some of the parents that were interviewed had children who had suffered an ADR that had not been reported through the Yellow Card Scheme. Following the interview, these parents were asked if they would like to now file a Yellow Card report, but all declined(69). Motivating and educating parents on reporting ADRs in their children could see a rise in the number of Yellow Card reports submitted, as well as increasing parental involvement in care.

This study observed that most of the ADR reports that were prompted by other members of staff were done so by doctors, the majority by consultants. Over half of the Yellow Card reports were also reported by doctors. However, it is possible that the individual tasked with reporting the ADR was not always the same person who first suspected the ADR, both using the Yellow Card Scheme and in this study. More research could be conducted to identify which individuals are most likely to detect ADRs in their roles within the wider care team, and how pharmacovigilance could be effectively integrated into the different roles fulfilled by an MDT.

It would also be interesting to see whether any neonatal ADR reports were submitted via the Yellow Card Scheme during the same nine-week period that the study observed. Given the rate of reporting during 2001 and 2010, it is likely that there would not have been enough reports to make a meaningful comparison.

A neonate-specific data collection proforma was designed for this study to allow the collection of all the data that was thought necessary for an informed causality assessment of the ADR. Yellow Cards reports often do not record some basic demographical information, such as weight. There is also no prompt to be specific about corrected gestational age, and both factors are known to influence neonatal pharmacology. Some of the Yellow Cards submitted did not report gender. This shows it is not only the quantity of neonatal ADR reports to the Yellow Card Scheme which is concerning, but the quality of information recorded too.

4.3.7 Summary

This prospective observational study has shown that ADRs occur in neonates and can impact their care. The spread of ADRs seen show that it is not only sick, preterm neonates that experience ADRs, and that some neonates will suffer multiple ADRs in a short time period. ADRs were observed to commonly prescribed drugs, some of which are used routinely for both diagnostic and therapeutic purposes. Although the focus of this study was on ADRs occurring to drugs prescribed directly to the neonate, some ADRs were observed as a result of drugs prescribed to the mother of the neonate during labour or pregnancy. A study focusing on these types of reactions alone could yield important results, and it is likely these ADRs would require unique evaluation methods. Additionally, a discrepancy between ADRs reported under research conditions and those being reported spontaneously is apparent. Educational and motivational interventions that are accepted by neonatal staff will be needed to improve reporting to encourage better pharmacovigilance for neonates.

Chapter 5: Causality assessment of adverse drug reactions in neonates

Once an ADR is suspected in any patient, it is important to evaluate the ADR as part of good pharmacovigilance. Some algorithms exist to help clinicians to assess ADRs and have been in use for 40 years. However, research shows that these tools rarely produce a reliable outcome when compared with each another, perhaps leaving the clinician thinking their own judgement may be just as accurate and less time-consuming(83).

The team who conducted the paediatric study (Adverse Drug Reactions in Children, ADRIC) found that existing tools were difficult to use to evaluate paediatric ADRs, particularly those occurring in paediatric in-patients. Neonates are likely to suffer similar burdens of ADRs, as has been described in the past and in the present(9)(46). This study evaluated the use of three causality assessment tools to determine their use for assessing ADRs in neonates.

Six assessors undertook three assessments each of 34 cases, resulting in 102 assessments per assessor and 612 total assessments. Each case was therefore assessed 18 times.

Table 16 shows the causality ratings assigned to each of the 34 cases by the six assessors. A chi squared test showed that the excess of definite ratings using the Du Lehr method was highly statistically significant, p-value < 0.001. This is suggestive of over-evaluation of causality of the ADR cases using the Du Lehr algorithm, leading to more neonatal ADRs being given definite ratings than would be agreed upon by expert consensus, or when using other methods of causality evaluation.

Table 16 Six assessors' causality ratings of 34 neonatal ADR cases using three different methods

	Karch and Lasagna algorithm					Du Lehr				LCAT			
Case Number	Unlikely	Conditional	Possible	Likely	Definite	Unlikely	Possible	Probable	Definite	Unlikely	Possible	Probable	Definite
1		1	2	3				3	3		4	2	
2		1	1	3	1		1		5		4	2	
3			1	4	1			1	5			6	
4			3	3				1	5		1	5	
5	3	2	1			1	2	2	1		4	2	
6	1	3		2				1	5		1	5	
7	1	1	3	1		2		1	3	2	2	2	
8		1	1	1	3				6		1	1	4
9				4	2				6			6	
10			3	1	2		2	1	3		3	1	2
11		3	2	1		1		2	3		4	2	
12			2	3	1				6			6	
13	1		4	1			1	1	4		2	4	
14	2	2	2			2		2	2		4	2	
15	5	1				5			1	2	3	1	

	Karch and Lasagna algorithm					Du Lehr				LCAT			
Case Number	Unlikely	Conditional	Possible	Likely	Definite	Unlikely	Possible	Probable	Definite	Unlikely	Possible	Probable	Definite
16	3	2	1			2	1		3	1	3	2	
17	1	3	1		1		1	1	4		2	3	1
18	4		1	1		4		1	1	1	3	2	
19	3	1	1	1		3		1	2	1	3	2	
20	1		2	3			1	1	4			6	
21		3	1	2		1		2	3	1	2	1	2
22		1	1	3	1			1	5			4	2
23		1	3	2					6		1	5	
24				1	5				6			1	5
25	2	3	1			3		3		1	3	2	
26	2	2	1	1		2	1	2	1	1	4	1	
27	1	2		3				3	3		2	4	
28	2	3		1		3	1	2		1	3	2	
29		1	2	3				2	4		3	3	
30	3	3				5	1			4	2		
31		1	4	1					6			6	

	Karch and Lasagna algorithm					Du Lehr				LCAT			
Case Number	**Unlikely**	**Conditional**	**Possible**	**Likely**	**Definite**	**Unlikely**	**Possible**	**Probable**	**Definite**	**Unlikely**	**Possible**	**Probable**	**Definite**
32	4	1	1			4		1	1	3	3		
33		1	1	2	2			1	5		1	3	2
34		3	1	2		1	1		4	1	1	4	
Grand total (n)	39	46	47	53	19	39	13	36	116	19	69	98	18
Grand total (%)	19.1	22.5	23.0	26.0	9.31	19.1	6.86	17.6	56.4	9.31	33.8	48.0	8.82
Number of 5 or 6s in each column	1	0	0	0	1	2	0	0	12	0	0	8	1

5.1 Inter-rater reliability

Table 17 shows the number of times each rating was given by each assessor using each of the three tools.

Table 17 Frequency of ratings per assessor per tool

Assessor	Tool	Unlikely	Conditional	Possible	Probable/Likely	Definite
BP	K+L algorithm	9	3	6	12	4
	Du Lehr	10	-	1	1	22
	LCAT	10	-	0	20	4
BY	K+L algorithm	9	10	6	8	1
	Du Lehr	11	-	3	4	16
	LCAT	5	-	9	17	3
BS	K+L algorithm	5	11	9	8	1
	Du Lehr	4	-	2	10	18
	LCAT	1	-	12	19	2
MT	K+L algorithm	10	8	9	5	2
	Du Lehr	7	-	4	6	17
	LCAT		-	20	13	1
DH	K+L algorithm	3	4	14	10	3
	Du Lehr	3	-	1	9	21
	LCAT	2	-	8	20	4
JM	K+L algorithm	3	11	3	9	8
	Du Lehr	4	-	2	6	22
	LCAT	2	-	11	17	4

Pair-wise kappa scores were measured between all six assessors using each of the three tools (tables 18, 19 and 20). Weighted kappa scores ranged from 0.148 to 0.454 for the Karch and Lasagna algorithm, 0.114 to 0.483 for the Du Lehr and 0.121 to 0.428 for the LCAT. The majority of weighted kappas for each pair-wise comparison for each tool corresponded to 'fair' inter-rater reliability.

Percentage exact agreement between the ratings given to each case by each of two assessors, ranged from 14.7% to 41.2% for the Karch and Lasagna algorithm, 38.2% to 58.8% for the Du Lehr tool and 26.5% to 61.8% for the LCAT. Extreme disagreement ranged from 8.82% to 35.3% for the Karch and Lasagna algorithm, 11.8% to 38.2% for the Du Lehr tool and 0% to 17.6% for the LCAT.

All of the assessors were most likely to assign the causality rating of 'definite' using the Du Lehr method. All but one of the assessors were most likely to assign the causality rating of probable using the LCAT. The Karch and Lasagna algorithm led to more varied assessments.

Global kappa scores were measured to outline the inter-rater agreement between all six assessors. These figures reflected the range of pair-wise kappas that were seen and can be found in table 21.

Table 18 Karch and Lasagna algorithm inter-rater reliability: red shading- 'poor' inter-rater reliability, orange shading- 'fair' inter-rater reliability, green shading- 'moderate' inter-rater reliability

			Assessor 1					
			BP	**BY**	**BS**	**MT**	**DH**	**JM**
Assessor 2	**BP**	%EA/ED		35.3%/32.4%	29.4%/ 20.6%	29.4%/35.3%	35.3%/32.4%	29.4%/23.5%
		Kappa score (95% CI)		0.177 (-0.012 to 0.366)	0.117 (-0.060 to 0.293)	0.113 (-0.067 to 0.293)	0.170 (-0.021 to 0.361)	0.130 (-0.043 to 0.303)
		Weighted Kappa score		0.328	0.311	0.207	0.264	0.348
	BY	%EA/ED			32.4%/8.82%	41.2%/14.7%	32.4%/34.3%	35.3%/26.5%
		Kappa score (95% CI)			0.113 (-0.100 to 0.327)	0.236 (0.021 to 0.451)	0.152 (-0.035 to 0.339)	0.188 (0.002 to 0.373)
		Weighted Kappa score			0.381	0.454	0.243	0.400
	BS	%EA/ED				29.4%/20.6%	38.2%/17.6%	23.5%/20.6%
		Kappa score (95% CI)				0.088 (-0.112 to 0.288)	0.196 (-0.018 to 0.410)	0.032 (-0.148 to 0.211)
		Weighted Kappa score				0.278	0.364	0.293
	MT	%EA/ED					17.7%/26.5%	35.3%/35.3%
		Kappa score (95% CI)					-0.044 (-0.205 to 0.117)	0.213 (0.030 to 0.395)
		Weighted Kappa score					0.148	0.284
	DH	%EA/ED						14.7%/29.4%
		Kappa score (95% CI)						-0.041 (-0.191 to 0.109)
		Weighted Kappa score						0.154
	JM	%EA/ED						
		Kappa score (95% CI)						
		Weighted Kappa score						

Table 19 Du Lehr inter-rater reliability: red shading- 'poor' inter-rater reliability, orange shading- 'fair' inter-rater reliability, green shading- 'moderate' inter-rater reliability

			Assessor 1					
			BP	**BY**	**BS**	**MT**	**DH**	**JM**
Assessor 2	**BP**	%EA/ED		55.9%/26.5%	58.8%/23.5%	50.0%/29.4%	58.8%/23.5%	58.8%/26.5%
		Kappa score (95% CI)		0.258 (0.027 to 0.489)	0.328 (0.132 to 0.523)	0.177 (-0.065 to 0.418)	0.272 (0.044 to 0.500)	0.237 (0.043 to 0.432)
		Weighted Kappa score		0.372	0.397	0.240	0.316	0.330
	BY	%EA/ED			55.9%/26.5%	52.9%/17.7%	38.2%/38.2%	50.0%/26.5%
		Kappa score (95% CI)			0.344 (0.134 to 0.555)	0.294 (0.076 to 0.513)	0.045 (-0.141 to 0.232)	0.208 (0.006 to 0.410)
		Weighted Kappa score			0.394	0.483	0.114	0.352
	BS	%EA/ED				44.1%/20.6%	52.9%/11.8%	47.1%/20.6%
		Kappa score (95% CI)				0.143 (-0.080 to 0.367)	0.193 (-0.076 to 0.462)	0.100 (-0.141 to 0.341)
		Weighted Kappa score				0.316	0.368	0.277
	MT	%EA/ED					47.1%/23.5%	52.9%/26.5%
		Kappa score (95% CI)					0.150 (-0.040 to 0.340)	0.234 (-0.006 to 0.473)
		Weighted Kappa score					0.240	0.316
	DH	%EA/ED						58.8%/20.6%
		Kappa score (95% CI)						0.240 (-0.016 to 0.495)
		Weighted Kappa score						0.218
	JM	%EA/ED						
		Kappa score (95% CI)						
		Weighted Kappa score						

Table 20 LCAT Inter-rater reliability: red shading- 'poor' inter-rater reliability, orange shading- 'fair' inter-rater reliability, green shading- 'moderate' inter-rater reliability

			Assessor 1					
			BP	**BY**	**BS**	**MT**	**DH**	**JM**
Assessor 2	**BP**	%EA/ED		50.0%/17.7%	41.2%/17.7%	26.5%/11.8%	44.1%/17.6%	55.9%/11.8%
		Kappa score (95% CI)		0.233 (0.033 to 0.434)	0.103 (-0.049 to 0.255)	0.047 (-0.057 to 0.151)	0.103 (-0.106 to 0.312)	0.346 (0.152 to 0.540)
		Weighted Kappa score		0.297	0.169	0.121	0.187	0.428
	BY	%EA/ED			55.9%/5.88%	55.9%/5.88%	61.8%/14.7%	52.9%/8.82%
		Kappa score (95% CI)			0.279 (0.040 to 0.517)	0.112 (0.103 to 0.541)	0.388 (0.137 to 0.639)	0.271 (0.026 to 0.516)
		Weighted Kappa score			0.356	0.355	0.368	0.345
	BS	%EA/ED				50.0%/0.00%	52.9%/0.00%	44.1%/5.88%
		Kappa score (95% CI)				0.133 (-0.155 to 0.422)	0.188 (-0.114 to 0.491)	0.065 (-0.222 to 0.352)
		Weighted Kappa score				0.213	0.327	0.142
	MT	%EA/ED					47.1%/8.82%	50.0%/2.94%
		Kappa score (95% CI)					0.164 (-0.068 to 0.396)	0.187 (-0.066 to 0.441)
		Weighted Kappa score					0.160	0.264
	DH	%EA/ED						50.0%/5.88%
		Kappa score (95% CI)						0.184 (-0.094 to 0.461)
		Weighted Kappa score						0.274
	JM	%EA/ED						
		Kappa score (95% CI)						
		Weighted Kappa score						

Table 21 Global kappa scores for six assessors using three causality assessment methods

Tool	Global Kappa	Confidence interval
Karch and Lasagna	0.157	0.0741 – 0.239
Du Lehr	0.254	0.139 – 0.369
LCAT	0.209	0.121 – 0.297

5.2 Inter-tool reliability

Weighted and non-weighted kappa scores were also calculated to measure the agreement when each assessor used different tools to assess the same 34 cases. This aimed to measure inter-tool reliability. There was significant variability between assessors, but some were consistent in their assessment regardless of the tool used. The highest kappa score was seen when comparing each assessor's ratings using the Karch and Lasagna algorithm and the LCAT.

Table 22 Inter-tool reliability: red shading- 'poor' inter-tool reliability, orange shading- 'fair' inter-tool reliability, green shading- 'moderate' inter-tool reliability, dark green shading- 'good' inter-tool reliability

Assessor		Karch and Lasagna and Du Lehr	Karch and Lasagna and LCAT	Du Lehr and LCAT
BP	Kappa score (95% CI)	0.218 (0.087 to 0.350)	0.580 (0.386 to 0.774)	0.319 (0.183 to 0.454)
	Weighted Kappa score	0.460	0.712	0.616
BY	Kappa score (95% CI)	0.257 (0.109 to 0.405)	0.261 (0.037 to 0.485)	0.255 (0.094 to 0.415)
	Weighted Kappa score	0.383	0.434	0.538
BS	Kappa score (95% CI)	-0.022 (-0.157 to 0.112)	0.102 (-0.118 to 0.321)	0.058 (-0.108 to 0.223)
	Weighted Kappa score	0.145	0.236	0.298
MT	Kappa score (95% CI)	0.109 (-0.037 to 0.255)	0.183 (-0.043 to 0.409)	0.030 (-0.071 to 0.130)
	Weighted Kappa score	0.246	0.360	0.239
DH	Kappa score (95% CI)	0.067 (-0.072 to 0.206)	0.409 (0.184 to 0.635)	0.071 (-0.100 to 0.242)
	Weighted Kappa score	0.227	0.533	0.285
JM	Kappa score (95% CI)	0.194 (0.021 to 0.367)	0.455 (0.234 to 0.676)	0.165 (0.004 to 0.325)
	Weighted Kappa score	0.348	0.591	0.338

5.3 Assessor view of tool usability

After completing the causality assessments, each assessor was asked to complete a brief questionnaire evaluating each causality assessment tool. The assessors were asked to rate four statements regarding the usability of each tool on a Likert scale. The collated results can be seen in figures 2 to 5.

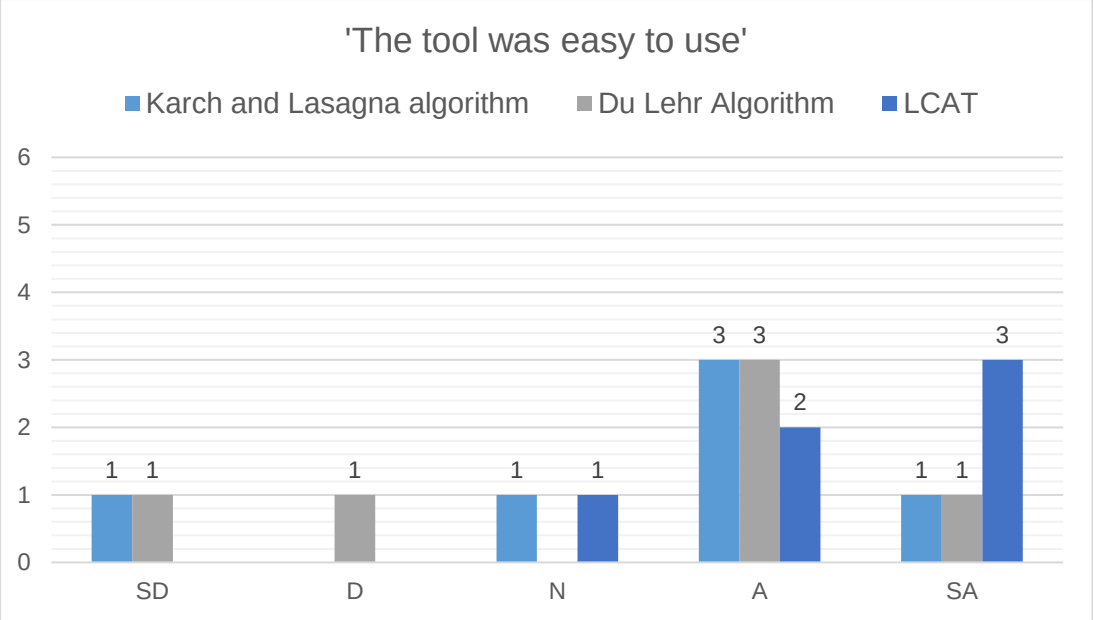


Figure 2 'The tool was easy to use' - assessor opinions regarding three methods

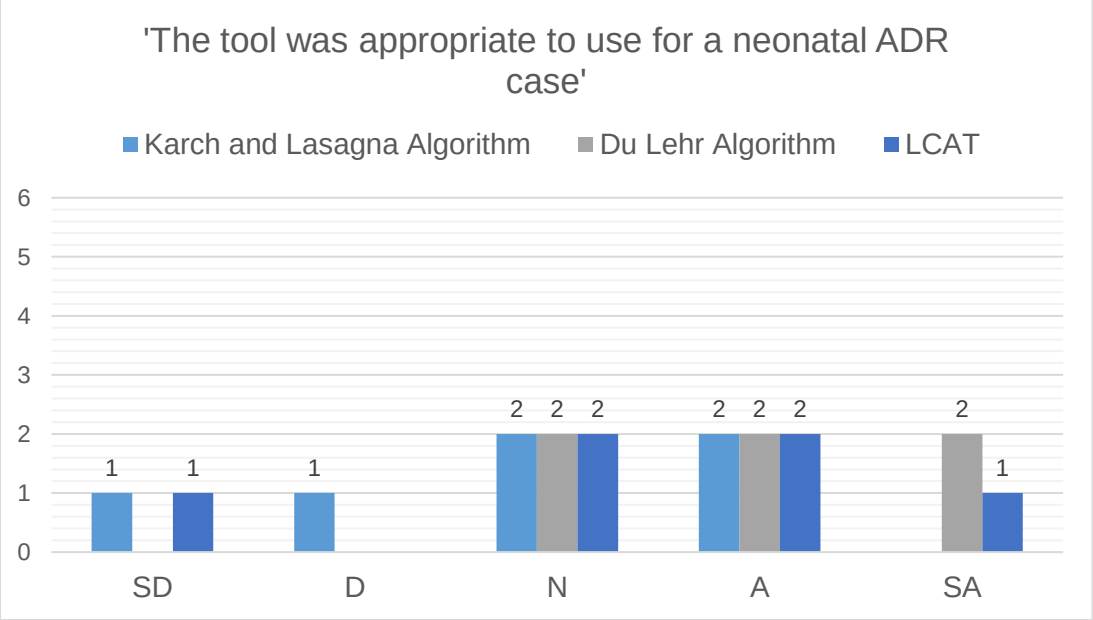


Figure 3 'The tool was appropriate to use for a neonatal ADR case' - assessor opinions regarding three methods

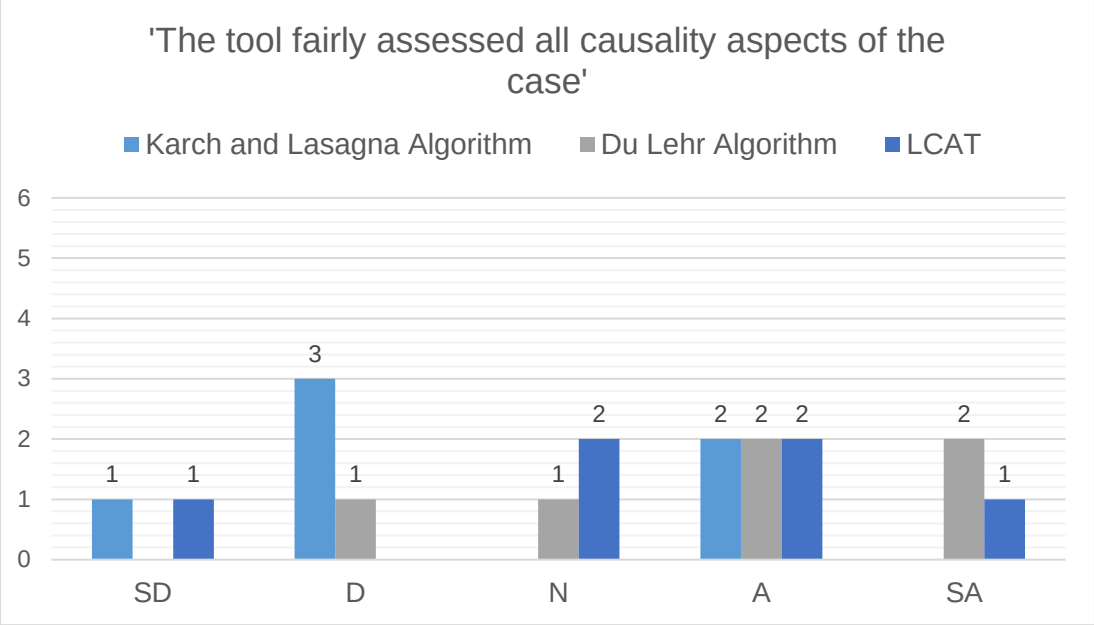


Figure 4 'The tool fairly assessed all causality aspects of the case' - assessor opinions regarding three methods

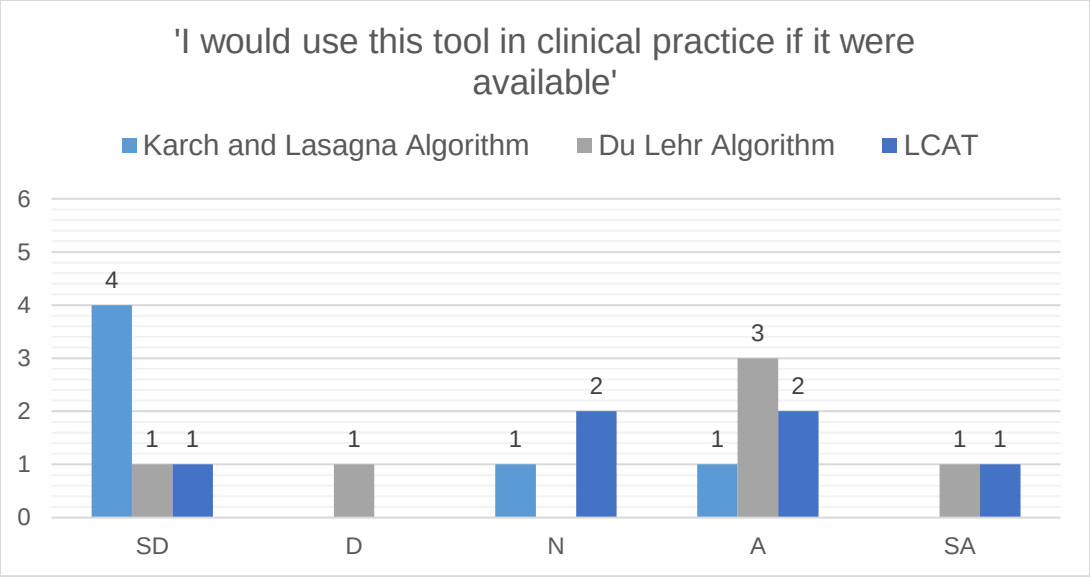


Figure 5 'I would use this tool in clinical practice if it were available' - assessor opinion regarding three methods

There was also opportunity in this questionnaire for free text regarding any aspect of the tool. Further to this some of the assessors reported their opinions verbally. Some commentary on the opinions has been shared below.

Karch and Lasagna algorithm

The Karch and Lasagna algorithm does not recognise the effect of changing the dose of medications as it only focuses on the effect of withdrawing or reintroducing the drug. This could lead the user to choose the option 'they don't withdraw the medicine and the ADR improves', taking away two points from the final rating. As there is no alternative option, a reduction in drug dose which sees an ADR improve would have to fit under this category, reducing the likelihood of causality from a seemingly positive association. ADRs associated with a permanent or long-lasting effect also have difficulty fitting into a category here. For example, an extravasation burn does not immediately improve when the drug is stopped and is likely to remain if the drug is started through a different line.

Sections F and G in this algorithm regarding 'contributing factors which favour the causal relationship' and 'extra examinations' were used in varying amounts by the different assessors, even though every assessor assessed the same cases. 'Contributing factors which favour the causal relationship' is open to individual interpretation, and some clinicians gave examples of what factors had led them to select the option; family history, timing of the ADR, improvements on stopping. Examples of 'extra examinations' used included abdominal x-rays and serum drug levels.

'New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units' algorithm (Du Lehr)

The 'New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units', like the Karch and Lasagna algorithm, requires the user to add multiple scores together to reach an outcome. The answer to each of the thirteen questions is weighted differently. To reach a rating of definite the assessor can score the reaction anywhere in the range of 14 to 51 whereas to reach a possible rating the score can only range from 3 to 6. The tool also allows limited answers to be given- yes, no or not applicable/unknown. Some of the questions lend themselves to a 'maybe' option, such as 'was the adverse event likely a change (exacerbation, recurrence, complication, or new manifestation) in a pre-existing condition?', yet this option is not available.

The Liverpool Adverse Drug Reaction Causality Assessment Tool (LCAT)

The LCAT appears the quickest tool to use as the clearly laid out flow chart leads the user directly to the outcome without the need for calculations.

Clinicians noted that it was very hard to reach a definite rating when assessing the neonatal ADR cases. The only way of reaching this outcome using the LCAT is if the neonate experiences a positive re-challenge of the suspected drug or has a history of suffering the same ADR. Whilst some neonates in the study did have histories of suffering the same or similar ADRs, this was usually in the less severe ADR cases. Re-challenges were rarely observed. Unlike the other tools, the LCAT does not provide an unknown option for all the questions. The assessors found this difficult for the questions 'was there a positive re-challenge?' and 'Is there a past history of the same event with this drug in this patient?'. Some of the ADR cases used in this study were experienced by neonates that were transferred to or from other hospitals throughout their care, and so the information regarding possible historical ADRs or re-challenges was not always available.

The question 'was the event associated with long-lasting disability or impairment?' may also not be appropriate for use in neonates given that these factors may not be able to be assessed for some years.

5.4 Discussion

The primary reason for collecting neonatal ADR data was to assess the use of three causality assessment tools to determine their appropriateness for neonatal clinical practice. A method which assesses the likelihood that a drug has caused a neonate harm, that is tested, population-specific and efficient, could greatly impact the health of neonates in the UK and other countries. If such a method were available in the everyday clinical care of neonates, clinicians could make informed decisions to adjust their prescriptions and reduce iatrogenic harm to this vulnerable population.

5.4.1 Causality assessment tools

In recent years, it has become apparent that many pre-existing ADR assessment tools are inappropriate for assessing paediatric ADRs. Recent attempts to overcome this have resulted in the creation of new tools, namely the Liverpool ADR Causality Assessment Tool (LCAT) created in ADRIC, and the 'New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units' created in the US(65)(67). The LCAT, although the product of a study into ADRs in children, was not designed specifically for this population. The 'New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units' (referred to here as Du Lehr) has never been validated in a setting outside of that in which it was originally created. The Karch and Lasagna algorithm is an older tool which was not designed specifically for the paediatric population, but has been used in a recent observational study of neonatal ADRs(46).

This study evaluated neonatal ADRs using the aforementioned tools, to determine whether any one, or a combination of different elements of each, is appropriate for use in a neonatal setting.

5.4.2 Inter-rater reliability

The results of evaluating the three causality assessment methods to determine their appropriateness for assessing neonatal ADRs show no clear optimum method. All three tools demonstrated only 'fair' inter-rater reliability when the tools were used by six different assessors to evaluate real neonatal ADR cases. There was little difference between the Kappa scores calculated to measure the pair-wise agreements for all assessors using each of the three tools. The Du Lehr method showed the lowest number of kappa scores corresponding to poor inter-rater reliability (*1*). Each tool only achieved one kappa score that corresponded to moderate inter-rater reliability. The global kappa scores showed the Du Lehr method demonstrated the best inter-rater reliability, but the score was only marginally higher than those for the other two tools.

The ranges of pair-wise weighted kappas were similar amongst all three tools. Only 6.67% of the kappas for each tool suggested 'moderate' inter-rater reliability. For the Karch and Lasagna algorithm 80% of the remaining kappas showed 'fair' inter-rater reliability with two kappas showing 'poor' inter-rater reliability. A third of the LCAT kappas suggested 'poor' inter-rater reliability. The use of a causality assessment tool has the potential to direct clinical decision making and influence medicines prescribed to neonates, so it would be hoped that at least a 'good' level of inter-rater reliability would be exhibited by a tool before its use is encouraged in clinical practice. When the ADRIC research team designed the LCAT, the tool was adapted several times before it resulted in a global kappa score of 0.6, suggesting 'good' inter-rater reliability, and was published(65). With the majority of pair-wise kappas indicating only 'fair' inter-rater reliability for all three tools, these tools may need to be adapted before they are appropriate to use in neonatal clinical care. The global kappa scores calculated in this study reflected the range of pair-wise kappas that were seen. The highest global kappa was for the Du Lehr algorithm, but each of the three global kappas only correlated to fair inter-reliability.

5.4.3 Inter-tool reliability

The highest inter-tool reliability was observed between the Karch and Lasagna algorithm and the LCAT; 20% of the pair-wise kappas exhibited 'good' inter-rater reliability, 40% 'moderate' and the remaining 'fair' (table 22). However, this does not necessarily mean that these tools are the most appropriate for use, only that they most often lead the user to the same outcome regardless of whether this outcome is an over or under-estimate of causality. This suggests that it is important to be consistent in causality assessment methodology within pharmacovigilance studies. Additionally, consistent use across pharmacovigilance studies would mean easier comparison between results. In the normal process of evaluating a new method it is compared to the current gold standard method. In the ADRIN study there was not a gold-standard causality assessment tool to compare the three tools to, so making a judgement about the efficacy of each tool was difficult. The Naranjo algorithm is a well-known method for assessing ADRs, but the very creation of the LCAT came about due to difficulties using the Naranjo algorithm to assess cases of paediatric ADRs collected in ADRIC(65).

To increase the precision of the estimates of the 'true' kappa scores, an ideal study would assess more than 34 cases. In the case of ADRIN, time limited the ability to do this, but the difficulty of finding enough assessors to commit to undertaking several hundred assessments must be a significant limitation in many studies.

5.4.4 Variability amongst causality assessment methods

For the sample of 34 ADRs, the use of different causality assessment tools yielded a range of outcomes for each case. Previously published studies into ADRs have only reported on the ADRs deemed probable or definite using varying causality assessment methods, so as to report accurate data that are most likely to be witnessed in other studies and neonatal populations. A systematic review into pharmacovigilance studies conducted in children found significant variation in reported data, particularly with regards to the causality and severity assessments conducted and the methods used for these(4). Many studies do not declare the method of causality assessment used or the reason for selecting a certain method. This study found that a different number of ADRs would be reported for publication using each of the three tools evaluated. This also differed between assessors.

If the Karch and Lasagna algorithm were used, the number of ADRs included in the reported data set would have ranged from 7 to 17 out of a maximum of 34 ADR reports, for the six assessors. For the Du Lehr this increased to 20 to 30 and the LCAT range was 14 to 24. Across the three tools and six assessors the percentage of ADRs that could have been included ranged from 20.6% to 88.2%. Of the 34 cases that were assessed for causality, there was only one case that did not receive at least one probable or definite rating by any assessor using any of the three tools.

This demonstrates that the method of causality assessment used in a study greatly affects the incidence rates and results reported, and thus the interpretations made by authors and readers. This difficulty also applies in deciding which ADRs to report to the MHRA. As there is no gold standard ADR causality assessment method specifically for the paediatric or neonatal population, it may be beneficial to encourage a universal way of presenting ADR data in this population.

Whilst the creation of a ‘perfect’ tool is awaited, it may be best to agree on the most appropriate tool to be used in all studies in the interim. This way, the results of studies would be easier to compare. An agreement on which tool to use in all pharmacovigilance studies conducted in neonates, and which results to report (i.e. all but unlikely ADRs), would make it easier to compare results and draw interpretations about differences seen. Whilst it may be hard to decide upon and enforce a universally accepted methodology, an alternative option would be to agree on a method of displaying ADR results so that they are open to interpretation and analysis by the reader; for example, declaring the causality assessment method, assessor designations and ratings given to each case by each assessor. This may be impractical in studies that assess hundreds or thousands of cases.

The different ratings were given in differing amounts using each of the three tools. For example, using the Karch and Lasagna algorithm and the Du Lehr tool the unlikely rating was given 39 times in each, but using the LCAT this rating was only given 19 times. One reason for this could be that one of the two ways to reach an unlikely rating using the LCAT is to answer no to the question 'do you suspect an adverse drug reaction?'. It would be hoped that this pathway would have been used infrequently in this study given that all the cases were collected following an original suspicion of an ADR, though differing opinions are to be expected. A definite rating was given using the Karch and Lasagna algorithm and the LCAT almost the same amount of times, 19 and 18 respectively. However, using the Du Lehr, 116 'definite' causality ratings were given, over 50% of all assessments. When the ADRIC team designed the LCAT they originally found the tool reached the 'definite' rating for 85% of the paediatric cases assessed. The tool was reviewed and adjusted because of this(65). However, it is not reported what ratings were given when the Du Lehr algorithm was tested on 50 ADR cases when it was first validated internally, and whether or not any adjustments were made because of this(67). The Karch and Lasagna algorithm showed the largest variance in ratings given. Only two of the 34 cases when assessed using this tool received the same rating from five assessors and all six assessors never perfectly agreed using this tool. However, when using the Du Lehr tool and the LCAT, five or more assessors gave the same rating for the same case fourteen and nine times respectively.

The Du Lehr algorithm produced the most definite ratings. A chi squared test produced a p value <0.001 suggesting that the excess of definite ratings seen when using this tool in comparison to the other two tools is highly significant. This suggests that the Du Lehr algorithm may be over-evaluating the neonatal ADRs to give more cases definite ratings than are rated definite by other tools, or by expert opinion. The LCAT was adapted when it was seen to produce an excess of definite ratings, but the Du Lehr method was not adjusted in this way(67). This may be a necessary adaptation to allow a fair evaluation of neonatal ADRs. When using the Du Lehr algorithm, the range of scores that all denote a definite rating is much wider than the range for those less likely ratings, so an adjustment in these parameters may lead to a more accurate assessment.

The LCAT gave mainly probable ratings and the lowest number of definite ratings of any of the three tools. When the numbers of probable and definite ratings from the LCAT are combined, the number is identical to the number of definite ratings given by the Du Lehr (*116*). This suggests that the probable rating in the LCAT and the definite rating in the Du Lehr are assessing a similar concept. A definite rating can only be reached using the LCAT if there is a positive re-challenge or the presence of a history of the same ADR. The history of suffering an ADR is not explored in the Du Lehr algorithm, and answering negatively to the question

regarding re-challenge only deducts one point from the total score, meaning a definite rating can still be reached through many permutations. When the LCAT was adapted due to suspected over-assignment of 'definite' ratings, it was these two concepts that were added to the pathway to reach a definite rating using this tool. It would be interesting to revisit the first version of the LCAT tool to see if this tool would be more appropriate for assessing neonatal ADRs compared to the current one, given that re-challenges and/or histories may be rarer in these younger children.

5.4.5 Variability amongst assessors

The six assessors in this study have different designations and backgrounds but all had experience in working in clinical neonatology. This methodology was thought appropriate as assessors used in the ADRIC research programme also had different roles e.g. pharmacists, doctors and nurses. There were some cases where one assessor was in extreme disagreement with the majority of the other assessors using one of the tools, namely cases 15, 18, 21 and 32. However the assessor who disagreed was different in every case. Unfortunately, although this was initially planned, time limited the ability of this study to recruit a wider variety of assessors, as all six assessors were doctors. It would have been interesting to see whether the inclusion of pharmacists and nurses would have changed the inter-rater reliability seen when using the three tools. However, in the wider use of causality assessment tools, designation of the user should not influence the outcome. An ideal tool should be able to be used by any health care professional, in any setting for assessing any ADR in any neonate.

There was variability in the number of times each rating was given by each assessor using each of the tools (table 17). Four assessors each gave four definite ratings when using the LCAT. However only one of the definite ratings from each assessor was given to the same case. As the questions regarding re-challenge and history are reasonably objective, previous questions in the flow chart must have caused the discrepancy in ratings here. The questions preceding the final question leading to a definite rating include 'what is the probability that the event was due to an underlying disease?' and 'was the event associated with long-lasting disability or impairment?'. Both these questions contain an element of subjectivity and can be difficult to assess in neonates who may be critically ill, and hence will likely have led to the difference in ratings given by the assessors for these cases.

Assessors BP and BY demonstrated moderate and good inter-tool reliability, showing that they were consistent in their interpretation and assessment of the cases. However, their inter-rater reliability scores were below average. This suggests that the assessors were assessing different concepts but each was consistent in their reasoning. Further clarification of some

aspects of the tools may help to avoid this, for example, objective definitions of some of the concepts, e.g. ‘contributing factors’ in the Karch and Lasagna algorithm.

5.4.6 Characteristics of cases

Some cases showed a large spread of results within and across all three tools, making it difficult to make a judgement of true causality. These cases were often the cases that were least well known with scarce previously published literature. It was also noted that for these cases there was not much documentation in the case summary of any alternative causes. Little evidence to rule out an alternative cause may have led the assessors to presume an alternative diagnosis was more likely.

There were two cases where the assessors showed almost perfect agreement using two tools, one when using Du Lehr and the LCAT and the other when using Du Lehr and the Karch and Lasagna algorithm, but showed a spread of ratings across three categories when using the third tool. When using the Du Lehr to assess these two cases however, the assessors showed perfect agreement on a definite rating. It was noted that these two cases both contained more than one reaction to the same drug, and it was perhaps this that reduced inter-rater reliability for this case. These cases could be considered more complex and this could imply that the Du Lehr applies the most general approach to assessing causality. Some clinicians explained that they found it challenging to assess those ADR reports where more than one reaction had occurred. However, on reviewing all the ADRs that were assessed it was found that there was variability in rating for some, but not all, of the cases involving more than one reaction. Some of the Yellow Card reports reviewed in this study also reported more than one reaction per report.

There were only three cases that showed some a majority agreement for an unlikely causality rating across at least two tools. For cases 15, 18 and 32 at least four of the six assessors agreed on an unlikely rating using the Karch and Lasagna and Du Lehr algorithms, but showed a spread of results when assessed using the LCAT. This may be due to the first question in the LCAT, ‘do you suspect an ADR?’. It was noted that these three cases detailed less well documented ADRs for which alternative explanations were more likely. There was most likely a suspected concurrent infection for one case, and the other two cases both occurred in extremely sick preterm neonates with multiple comorbidities. Case 30 demonstrated the most convincing majority rating of unlikely, with all six assessors using all three tools only choosing unlikely or conditional/possible ratings.

When reviewing the assessments of individual cases, it is possible to hypothesis why different tools resulted in different outcomes.

Case study one

The case of antibiotics leading to thrombocytopenia- case 21. This case, when assessed by one assessor, received a possible rating when using the LCAT and a definite rating using the Du Lehr algorithm. The final question when using the LCAT which leads the user to a possible rating is 'Is there any objective evidence supportive of the causal ADR mechanism?'. As there is no such evidence for this case, the assessor cannot select another path and thus the possible rating is reached. Whilst questions 12 and 13 of the Du Lehr tool are similar to this question, answering them negatively does not exclude any causality outcome, and cases can still be given definite ratings, as seen in this case. In general, this case appeared difficult to assess amongst all assessors, receiving each of the five available outcomes at least once.

Case study two

Another interesting case was the report of a cerebral haemorrhage occurring after the administration of inotropes- case 32. Using the Karch and Lasagna and Du Lehr algorithms the case was assessed as being unlikely four out of six times. However, when using the LCAT it received the possible rating three times (three others unlikely). Using the LCAT, the case is automatically given an unlikely rating when the assessor chooses not to suspect an ADR. It is presumed that this was how this rating was reached, given that the only other way of reaching an unlikely rating, (by answering negatively to 'did the event appear after the drug was administered or dose increased?') should not apply to this case. There must have been some information in the case summary that lead two assessors to suspect an ADR. As two assessors chose to suspect an ADR, the case was assessed as possible. It would have been interesting to observe whether all the other assessors would have reached the possible outcome had they chosen to suspect an ADR. Both the Du Lehr and the LCAT require objective evidence to answer certain questions; the Du Lehr requires confirmation of an alternate aetiologic candidate and the LCAT requires evidence supportive of the causal ADR mechanism. These questions seem the opposite of each other. Both lead to a more likely causality rating when answered appropriately in favour of an ADR. With respect to the question in the LCAT, evidence in support of an ADR is much less likely in neonates than in other age groups because of the smaller knowledge base about the effects (intended and unintended) of medicines on neonates. On the other hand, with respect to the Du Lehr algorithm it is likely that a clinician will be able to consider multiple differentials for a clinical problem. Despite this case seeming to be thought unlikely by most assessors, it still received one definite rating using the Du Lehr algorithm.

Case study three

Extravasation reaction- case 18. Using the Karch and Lasagna algorithm and Du Lehr algorithm, one assessor rated the case as likely and definite, whilst all other assessors found

the case unlikely. Using the LCAT produced more variability in rating, finding the case unlikely, possible and probable. As with case study two, presuming the question 'did the event appear after the drug was administered or dose increased?' was answered accurately, the assessor who gave this case an unlikely rating must not have suspected an ADR. As no definition of an ADR was given to the assessors before undertaking the assessments, this suggests that different clinicians have differing opinions of what constitutes an ADR and may have believed an extravasation reaction to not be an ADR.

Case study four

The case of digoxin suspected to have caused heart block was consistently rated as probable or definite by all six assessors using all three tools- case 9. There were some defining features of this case that are likely to have made this possible. This case was the only one which included a documented serum drug level. This, combined with a finding from an imaging investigation, provided objective evidence to the assessor and reduces the need for clinician opinion on concepts such as alternative diagnoses and evidence supportive of the causal ADR mechanism. Other cases that were given mainly definite ratings across all three tools were well known ADRs or had a positive history of an ADR following previous exposure to the drug in the neonate concerned.

5.4.7 Usability

It is very important to acknowledge the opinions of practising clinicians on tool usability when considering implementing such a resource into the busy daily routine of clinical care.

The data collected on the assessors' opinions regarding the usability of each of the tools shows a slight preference for the Du Lehr algorithm as a tool to use in clinical practice, with the LCAT also seemingly more preferred than the Karch and Lasagna algorithm. Even though addition is required when using the Du Lehr algorithm, and the LCAT scored better on ease of use, the Du Lehr scored best with regards to its ability to appropriately and fairly assess a neonatal ADR case. To properly assess clinician opinion on each of the three tools their use should be trialled by a greater number of assessors. Opinions may differ depending on setting; the LCAT is perhaps easier to use quickly on a ward round, whilst the Du Lehr or Karch and Lasagna methods may be more appropriate for group discussion in an MDT.

Overall, the range of opinions exhibited by the assessors throughout the questionnaire makes it difficult to determine if one tool was preferred overall. It may be a challenge to design a tool which is accepted by a wide range of users. However, five of the six assessors said that they would use at least one tool in clinical practice, showing practising clinicians are receptive to introducing a method of further evaluating neonatal ADRs.

All the tools require an element of 'previous knowledge' which is likely to vary between clinicians and their experiences. Answering questions regarding previous documentation of ADRs may require the use of the BNF which costs the clinician time. In addition to this, rarer or less well-known ADRs are more likely to be ignored if they generate unlikely causality ratings. This goes against the purpose of reporting less well-known suspected ADRs to the MHRA to understand more about drugs which may have very little safety information.

5.4.8 Question adaptation

The combination of statistical analysis and the opinions of the assessing clinicians suggests all three tools could be improved to be more suitable to use in the neonatal population.

The Karch and Lasagna algorithm currently does not recognise the impact of reducing the dose of a drug. 'Withdrawal' is interpreted as stopping a medication altogether, but a slight adjustment in this tool to 'withdrawal/dose reduction' may produce a fairer outcome.

The LCAT uses the question 'was the event associated with long-lasting disability or impairment?'. The follow-up of neonates that are born prematurely or experience medical or surgical conditions may continue for several years, thus making it difficult to fully answer this question when assessing a recent ADR in a neonate. If a timescale were applied to the question, or if it were adjusted to read 'do you suspect the event may result in long-lasting disability or impairment?', it could be better applied to the neonatal population. This would however, incur another subjective question, potentially further reducing inter-rater reliability. The long-term impact of ADRs in neonates, and the possibility that some ADRs may prove beneficial in later life, is an area of pharmacovigilance research that needs further exploration.

The presence of a history of an individual suffering an ADR, or a positive re-challenge, greatly increases the causality. However, it can often be difficult to assess these factors in neonates who may be a matter of days old and in whom re-challenges are often not ethically justifiable. All three tools assess one or both factors and place great importance on them. In the LCAT, a positive history or re-challenge is the only way to reach a definite rating. A more suitable route of reaching a likely causality outcome may need to be considered for this population. From this point of view, the Karch and Lasagna algorithm and 'New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units' tool could be considered more appropriate to use in the neonatal population as they still allow a 'definite' causality result to be reached in the absence of a positive history or re-challenge. However, the terms used in these concepts are not clearly defined in these tools. There is no explanation of how long after the initial dose of drug a subsequent dose must be given to be classified as a re-challenge. At some point, there must be a change between suffering an ADR because of a re-challenge and suffering a subsequent episode of an ADR for which there is a history. Harmonising these

definitions may present challenges in a population where a few weeks in age difference represents significant changes in pharmacokinetics and pharmacodynamics.

The first question in LCAT, ‘do you suspect an ADR?’, leads straight to unlikely if answered negatively. It could be argued that this defeats the aim of using causality assessment tools and does not prompt a clinician to consider an ADR. It could be thought a wasted question when a clinician not suspecting an ADR is unlikely to use the tool in the first place.

The variation in how the Karch and Lasagna algorithm was used by the different assessors suggests further clarification may be needed to improve its reliability. This is particularly apparent in sections F and G (contributing factors which favour the causal relationship and extra examinations) where for the same set of cases, the number of times F and G were used varied greatly between assessors. Some examples of which things justify points in these sections are given, but it is widely open to user opinion. Causality tools are most helpful if they lead users to a result which can be reached consistently amongst a group of users whose opinions may have differed had the assessment been made by personal judgement alone.

The Karch and Lasagna algorithm allows the user to select one of several options for each section of the assessment whereas the Du Lehr algorithm only allows the user to select ‘yes’ ‘no’ or ‘unknown’. The LCAT only provides the ‘unassessable’ or ‘unsure’ option twice. Whilst a limited amount of options reduces the variability between assessors, some cases may go unassessed if they do not fit into the available options. This could lead to the dismissal of a case if it is not able to be assessed for causality. For example, the questions regarding positive re-challenges and histories both only allow a yes or no answer. However, the nature of neonatal care is such that neonates are sometimes transferred between care, and the answer here may not be known. As there is no unknown option, the user is left to decide for themselves what action to take, and some may choose to discontinue the evaluation altogether. In respect to this difficulty, the other two tools are advantageous as the answers to other questions supersede difficulty answering some questions. However, three of the six assessors ‘strongly agreed’ that the LCAT was easy to use, whilst the other 50% either ‘agreed’ or ‘neither agreed nor disagreed’. Designing a tool which is both effective and accepted by clinicians in everyday practice will take careful planning.

The results presented in this study suggest that no one tool stands out as being the optimal method to be implemented into clinical practice in its current format. From the analysis performed it has been observed that there are benefits and flaws of different aspects of each tool including design, ease of use and questions. However, despite the difficulties that have been highlighted, each of the tools were able to assess neonatal ADRs, and show scope to be adapted, to improve their specificity for neonatal ADRs, and inter-rater reliability. Combining

optimal elements of each method into a new tool could also be successful. The slight improvement in inter-rater reliability seen when using the Du Lehr algorithm suggests neonate-specific methods are advantageous. Following on from this, questions that are difficult to apply to this population, such as those regarding re-challenge and history, could be removed or adapted so as not to be defining. Questions with more than yes and no outcomes, such as those in the Karch and Lasagna algorithm, will assess the broadest range of ADRs. Subjectivity of use could be reduced by using clear definitions and examples. Whilst needing to use calculations and/or the BNFc may reduce usability, a compromise regarding this may have to be reached to allow accurate ADR assessment.

5.4.9 Wider applications

Effective causality assessment methods would have wide benefits for paediatric pharmacovigilance. In one of the only other known prospective studies observing neonatal ADRs, Belén Rivas reported that the causality assessment of the ADRs observed was the study's main limitation. They also comment on difficulties labelling cases as definite without re-challenges, and underestimation of the incidence of ADRs because causality assessments deem them less likely(46). ADRIC made the decision to exclude paediatric patients in intensive care because the causality assessment was too difficult in this cohort(17). By the very nature of neonatal care, a large proportion of neonates will be cared for in intensive care, only further demonstrating that population-tailored assessment tools would benefit this population greatly. As pharmacology is also affected by concurrent illness, it may be necessary to have yet another method of assessing ADRs in these sickest of children, but there are resource implications.

Clinicians will always have differing opinions in all elements of clinical practice, so an optimal causality tool would need to account for these variations. However, one perspective is that the design of causality assessment tools will not be able to be improved much beyond their current abilities, and instead the investigation of ADRs as a possible differential diagnosis should be improved. The cases that saw the best inter-rater agreement were those with objective evidence, such as drug serum levels or imaging investigations. Increased investigation of possible ADRs would help to generate awareness amongst clinical staff and subsequently lead to better causality assessment and reporting. However, increasing the investigation of suspected ADRs will rely on improving clinician understanding and appreciation of ADRs in neonates.

5.4.10 Summary

In summary, this study has highlighted that the three evaluated causality assessment methods differ in their approach to assessing ADRs, leading to varied assessments of neonatal ADR

cases. Only one of the three tools was designed to be used to assess neonatal ADRs. Difficulties were faced when trying to apply some of the questions in the other two tools to this unique population. This, coupled with the improvement in inter-rater reliability seen when using a neonate-specific method, suggests that a population-specific method could be advantageous. A wide range of assessments seen for individual cases suggests that both the ADR in question, and how to use the tools, were interpreted differently by each assessor. It will be challenging to design a tool that can adjust for this inevitable difference in opinion, whilst still being acceptable and efficient for use in clinical practice. Some aspects of the evaluated tools have the potential for adjustment to improve their use for the neonatal population, and the wider implications of designing an appropriate causality assessment method for this population have been discussed. This study has highlighted the need for an effective method of assessing the causality of neonatal ADRs. A full evaluation of such ADRs will also require severity and avoidability assessments, and future research focussing on these areas will help to bring pharmacovigilance in neonates in line with that of older populations.

Chapter 6: Strengths, limitations, future research and conclusions

The ADRIN study has explored a new area of pharmacovigilance in neonates. As the number of studies describing ADRs in neonates is increasing, optimal methods for evaluating neonatal ADRs need to be identified to be able to evaluate the findings of such studies. This study has characterised three causality assessment methods and provided an insight into how suitable the three methods are in their current format. Beyond causality assessment, there are other ways in which a neonatal ADRs should be evaluated, and different population-tailored methods of doing this should be explored in future research.

6.1 Strengths of the study

6.1.1 Study design

Many previous studies into ADRs in children have been conducted retrospectively whereas this study was conducted prospectively. Observing ADRs prospectively allowed the researcher to capture the progression of an ADR as it developed. Any uncertain information could be queried with the medical staff caring for the neonate at the time an ADR was suspected. Retrospective pharmacovigilance studies often face limitations with omissions in data that would have been of value. This was found when reviewing Yellow Cards, many were missing basic demographic information(6). Prospective observation collects data that reflects recent practice, which is useful to those reviewing the literature. It would have been difficult to test the causality assessment methods on retrospectively collected ADR cases. In the first instance, it is likely that it would be difficult to find a large enough source of previously collected neonatal ADR cases. Secondly, any such sources, for example Yellow Card reports, may not contain a spread of ADRs that will range from unlikely to definite in causality.

The methods used in this study were piloted before data collection began. This included the method of detecting and collecting ADR cases and the causality assessment processes. From these pilot activities, changes were made to the data collection materials, which prompted the collection of additional data that influenced the causality assessments made. Moreover, exposure to the neonatal clinical setting educated the researcher in neonatal medicine and ADRs.

Conducting the prospective observation at the Liverpool Women's Hospital NICU was advantageous as this is a large tertiary unit seeing a range of cases. Despite the data collection period being much shorter, the number of neonates observed in this study was almost two thirds of the number of neonates that were observed in the one year data collection period in Belén Rivas' recent study(46).

The researcher who collected data on suspected ADRs was a medical student completing a master degree between the fourth and fifth years of training. Having no clinical involvement in the care of the neonates, the researcher could focus solely on looking for possible ADRs without any pressures to fulfil other roles.

In the ADRIC study the causality assessments were carried out at consensus meetings. In this study in neonates, the assessors were given paper copies of the assessments to complete in their own time and they could contact the researcher should they want more information from the complete case data. At consensus meetings assessors may be influenced by the opinions of the other attendees, so the methods used in this study avoided this bias. It was felt that independent conduction of the causality assessments best reflected how the tools may be used in clinical practice.

6.1.2 Aims of the study

The aims of the study targeted one methodological aspect of evaluating neonatal ADRs, through causality. This focused approach worked well in the limited time and meant a significant number of assessors could commit the time to performing over 100 assessments each. Had severity and avoidability methods also been evaluated, it may have been necessary to divide the group of assessors. As a result, using only two assessors to evaluate each assessment area, it would not have been possible to demonstrate the range of inter-rater reliability seen and the potential influence of the different profiles of the assessors. Evaluating only causality meant three tools could be compared.

Another strength of this study was the recruitment of assessors with a range of experience. This provided a good reflection of how the tool would function if used in clinical practice, as it would be used by health care practitioners with differing roles and amounts of experience. Secondly, the assessor opinions that helped to provide an assessment of the worth of each tool varied greatly, and it is likely that some of this variance was due to differing profiles of the assessors.

6.1.3 Scope for further research

The results of the ADRIN study are novel, but the research has also highlighted pathways for subsequent studies. There was a significant amount of other data collected that could be further analysed. Secondary to this, the cases collected may be a useful source for other studies designing new methods of ADR assessment, and a collaboration of this nature has already been explored with regards to severity assessments. The exploration of the causality assessment methods has identified areas of research that could subsequently be undertaken to create effective causality assessment methods for neonatal pharmacovigilance.

6.2 Limitations

6.2.1 Study materials and resources

Analysis of patient notes provided most of the data collected in this study. The electronic notes system used on the neonatal unit was BadgerNet. Paper drug charts were reviewed where necessary to complement this source. The validity of the data may have been improved if collected on a unit where electronic prescriptions are used. BadgerNet also does not allow access to mothers' records which would have facilitated the collection of data regarding maternal drug use, pregnancy history, labour history etc.

The data collection was undertaken by a single researcher whilst members of staff on the neonatal unit had the opportunity to contribute by informing the researcher of suspected ADRs through the ADR alert forms or notification in person. Having only one researcher to collect data meant it was not possible to continuously monitor all activity on the unit. Additional researchers to collect data would have facilitated daily attendance at both ITU and HDU ward rounds, a chance to attend ward rounds seven days a week as opposed to four, and a greater number of patients' notes being reviewed for ADRs each day. The ADRIC research programme had a team of researchers to collect data, and more sophisticated databases which allowed some data to be collected automatically. Additional researchers for this study would have enabled multiple sites to be observed. There were two local hospitals that could have been included in this study: a children's hospital which cares for neonates post-surgery and on a paediatric intensive care unit, and a local district general hospital with a tertiary neonatal unit. Having at least one researcher based at each of these hospitals would have allowed for a larger data set, as well as enabling comparisons to be made between the data sets from each hospital.

6.2.2 Underreporting

There is a vicious cycle whereby a lack of understanding about neonatal pharmacology leads to less concern regarding ADRs and less research into pharmacovigilance. This, coupled with the absence of materials available to help detect and assess neonatal ADRs, sees ADRs dismissed as inevitable and unpreventable problems of neonatal care. With further education and resources these issues could be overcome, but there will always remain a challenge when trying to detect the 'signal amongst the noise' when it comes to ADRs in sick neonates.

Disappointingly in ADRIN, the ADR alert forms were only used twice in nine weeks. The number of ADR reports prompted by other clinicians (16), was more encouraging but still only accounted for 25% of the total number of ADRs reported. The observational study, including the implementation of the ADR alert forms, was introduced every day for one week at both the

doctors' and nurses' handover at the beginning of the study, so it was hoped that most staff would have been aware of the ADR alert forms. This was in addition to introductions, posters, flyers and researcher presence throughout the study period. This low rate of reporting by other staff is likely to be multifactorial. Lack of confidence in ADR reporting, poor understanding of the definition of an ADR and limited time due to other clinical priorities are just a few of these factors.

There are always going to be challenges in introducing an activity which draws attention to harm to a patient, which has resulted from attempts to cure and care, and which may not be rectifiable by those reporting the harms. ADRs are often unpredictable and unavoidable, but this does not mean those involved do not feel guilt. Though ADRs are different from medical errors, some individuals may feel responsible for the outcome.

The level of staff involvement in the ADRIN study suggests further efforts are needed to make ADR reporting a routine part of everyday clinical practice. A qualitative study evaluating the opinions and experiences of clinical staff regarding ADRs and pharmacovigilance practices could help to identify why reporting is so low. By interviewing staff who spend the most time caring for neonates, the level of understanding about pharmacovigilance, as well as individual suggestions for improving the knowledge base and motivation could be captured. This would help to decide the most effective engagement strategy to improve reporting practices.

6.3 Future research

ADRIN has contributed to the data set involving neonatal ADRs, but there is significant scope for further research in this area. Beyond the detection of ADRs in neonates, this study has demonstrated the difficulties in performing causality assessments of neonatal ADRs using currently existing methodologies.

6.3.1 Extending ADRIN

If more time and funding were available, the scope of this study could be significantly broadened. Ideally, the data collection period would be extended to a minimum of one year. This would increase the number and range of ADRs observed, and allow for the follow up of cases for a longer time, providing a more valid assessment of aspects of the cases such as re-challenges, histories and the evolution of signs and symptoms. Even further time would allow for the conduction of the proposed systematic review, enabling a full examination of pharmacovigilance studies in neonates worldwide. A minimum of two full-time independent staff to collect ADR cases would increase the number of suspected ADR cases and make the detection process more thorough. Employing extra research staff would also allow for the collection of data regarding all babies, including those who are not suspected to have suffered

an ADR. The ADRIC study employed pharmacists to carry out the ADR detection process, and as this was a success, pharmacists could also be used to collect neonatal ADR data. If possible, feedback from the pharmacists who collected data for the ADRIC study could help to train staff, to learn from their experiences and create an effective detection method. If it were possible for electronic prescribing to be initiated on the unit, the validity and accuracy of data collected regarding drug prescribing would be likely to improve. Data collection could be further legitimised by gaining access to maternal notes. An electronic database that could automatically draw information from all of these sources would save time, increasing that available for ADR detection. This was successful in ADRIC.

Additional funding could be used to trial various staff motivational and educational interventions to examine their impact on increasing ADR reporting. This could include educational learning days for all ward staff and incentives to report suspected ADRs. Investment into exploring the opinions of parents regarding ADRs and encouraging their input into pharmacovigilance could also obtain interesting results in this novel area of research, and may boost ADR reporting.

With regards to the causality assessment process, an ideal panel of assessors would be recruited externally. More time and funds would allow for a variety of different assessors to be sought, including pharmacists, who could be trained together in the process of causality assessment. The same, or different, assessors could also complete severity and avoidability assessments to broaden the evaluation of ADR cases.

Despite there being many ways in which this study could have been improved with more funding and time, the core design of the study was successful and has provided an example of an effective method of studying ADRs in neonates, and its results. The prospective study design proved an advantageous way of collecting neonatal ADR data, and so even with extra resources, prospective data collection should still be followed where practical. The data collection proforma that was designed for this study is transferable to other settings and has the scope to be adapted for electronic use. The main benefit of extra resources to this study would be in the increased detection of ADRs and the wider promotion of pharmacovigilance in a vulnerable population.

6.3.2 Identifying ADRs in neonates

In order to encourage ADR reporting in neonates, effective methods for identifying neonatal ADRs will need to be implemented. In ADRIN, the observational approach was effective when conducted by a standalone researcher, but more efficient methods may be necessary to integrate pharmacovigilance into busy clinical environments. Both the BNFc and Yellow Card

Scheme are now available as electronic systems, and the use of computerised surveillance methods of ADR detection have been trialled in adult and paediatric populations(84),(85).

The merit of a computerised system has its basis in the detection of changes in laboratory investigations before changes in clinical signs can be detected. The difficulty with this in the neonatal population is that the physiological parameters considered normal for this age group are poorly defined. For example, where a rise in liver enzymes could be a signal of drug hepatotoxicity in adults, relatively high levels of liver enzymes are seen in sick preterm neonates with a number of different conditions(86). Ongoing work in this field will help to define the parameters of normal physiology in neonates such that the use of a computerised method of ADR detection in this population may be possible, which could help to reduce underreporting in this busy clinical setting. However, the aim of a computerised system should be to alert staff to possible ADRs that may need reporting, simultaneously increasing education, not to remove the responsibility of reporting ADRs altogether.

Promoting parental reporting of ADRs also has the potential to reduce underreporting, as there is a philosophy that no one is more expert in a child than their parents. Qualitative studies have suggested that parents are often disappointed with the communication they receive regarding side-effects of medicines administered to their child. However, opinions were positively different in parents of children in an oncology setting, suggesting that those clinicians using the most potentially harmful medications may be better at communicating the associated risks(87). This could also be the case in a neonatal setting, but opinions of parents have not been explored as greatly in neonatal units. Difficulty arises where pharmacology knowledge is lacking as there is a fine balance between being honest with concerned parents and withholding uncertain information that may generate unnecessary worry. A clinician may need to make a judgement of this based on each unique family, the condition of their child and other aspects of the family dynamics e.g. other siblings and emotional, social and financial strains. In neonatology, it may even be possible to discuss this concept in antenatal counselling. However, this study has shown that opinions regarding the causality of ADRs differs greatly between clinicians, and therefore not receiving information regarding ADRs may be preferable to hearing mixed opinions.

6.3.3 Understanding ADRs in neonates

Over the past few decades an increased amount of research into monitoring and reporting ADRs and promoting paediatric medicines research has led to improved medicines for children. However, there is still some way to go in understanding why individuals suffer ADRs, and this activity was not undertaken in this first ADRIN study. Future research could focus on the long term follow up of neonates suffering ADRs to analyse whether any beneficial

outcomes occur following ADRs. Conversely, drugs which appear to be beneficial in the short-term may give rise to long-term effects. Making parents aware of ADRs and the possible long-term effects of medications means they could monitor and report suspected long-term drug effects in their child that may not be detected by the clinicians who cared for them as a neonate.

Pharmacogenomics is an area of medicine which is of growing interest in many specialties. Pharmacogenomics refers to the influence of an individual's genotype on the action of a drug and the risk of ADRs. Future work into pharmacogenomics in paediatrics could help to increase the safety of drugs in children. However, as with most aspects of paediatric medicine, there are differences in this population which mean different pharmacogenomics studies and methods will need to be designed compared to those already tried in adults. For example, the expression of certain genes changes with age and development.

6.3.4 Evaluating ADRs in neonates

ADRIN has demonstrated that further work needs to be conducted to create effective methods of evaluating ADRs in neonates. This could include the adaptation of currently existing tools, such as those evaluated in this study. Identification of aspects of current tools that need to be adapted to optimise their use will be needed, and some suggestions have been made in this work. In addition to this, encouraging the creation of new neonate-specific tools should be encouraged, or at the very least paediatric-specific tools. However, any newly proposed methods will need to be tested on neonatal ADR cases, and these take time to identify and record. The lack of a gold standard method of assessing ADR causality in children makes it difficult to measure the efficacy of newly proposed methods as there is no current standard practice. If an effective method of assessing causality of ADRs in the neonatal population were to be designed, its implementation into clinical practice could help to significantly reduce the current level of underreporting being seen.

A full evaluation of an ADR should also include severity assessment. A team of investigators based in Belgium have recently been working on a tool to assess the severity of adverse drug reactions in neonates. The tool was created with the aim of creating a method to better assess ADRs occurring in clinical trials. However, there is no reason why it would not be helpful in assessing ADRs occurring in routine neonatal care.

Contact was made with the research team who created the tool to attempt some collaborative work in validating the proposed tool. The latest version of the tool was made available to see whether it could be used to assess the severity of the cases collected in the prospective observational study. Upon review by the research team it became apparent that the information in the case summaries used for the causality assessments was not adequate to

complete severity assessments using the proposed new tool. However, the process of collecting the extra information needed from the electronic notes was piloted by the principal investigator and a method for extracting the extra information was created in the form of an excel proforma. It is hoped that future work can be conducted using the cases collected in the ADRIN study to continue this collaboration. Having both a causality and a severity assessment of an ADR produces a more thorough evaluation and helps to highlight those cases that may be less well known but just as important to acknowledge and act upon. For example, a causality assessment alone may see possible ADRs being put aside, but possible severe ADRs may deserve more attention than those that are likely but mild.

It is unfortunate that there was not time to assess avoidability in this study. This evaluation would have been very interesting in the neonatal population where fewer tested drugs are available to treat very sick neonates. It may be that many neonatal ADRs are unavoidable due to the lack of tested alternative medicines. However, the underreporting of neonatal ADRs means that the there is a lack of information for the MHRA to identify where alternatives may be necessary.

6.4 Conclusion

In conclusion, this work has demonstrated that the three tools evaluated do not reliably assess neonatal adverse drug reactions, which occur at a significant frequency, and are different to those exhibited by older children and adults. Marked inter-rater variability was seen across all three tools when pair-wise and global comparisons were made between the ratings assigned to the same cases by six different assessors. The potential benefits of neonate-specific causality assessment methodology have been demonstrated by the difficulties encountered using general methods to assess the neonatal ADRs collected in this study. However, even a method designed specifically for assessing neonatal ADRs was shown to have only ‘fair’ inter-rater reliability and appeared to over-estimate the causality of ADRs when compared to other methods.

Measuring inter-tool reliability identified that varying the method of causality assessment used can give rise to unreliable results. Whilst some assessors showed internal consistency, the majority did not, suggesting that the consistent use of one method, within and across future neonatal ADR studies, will produce the most reliable results. This is supported by the differing amounts of use of each rating by each tool; the Du Lehr and the LCAT saw similar numbers of definite and probable ratings respectively, suggesting that they were assessing the same concept.

The three tools all exhibit different formats which influenced how the tool was used by each of the assessors, and their opinions on the usability of the tool and likelihood of successful

implementation into clinical practice. In general, it will be a challenge to design a tool appreciated by all users, but there are some aspects which were disliked or liked by the assessors in this study. Designing a new tool should consider clinician opinion as well as practical issues such as time necessary to use the tool and any additional requirements which may discourage use, such as calculations or requirement of a BNF. Any newly created methods need to be evaluated and validated both internally and externally. These processes could take significant time and expertise, but carrying them out could help to significantly boost ADR reporting and consequently improve the safety of medicines for this vulnerable population.

The ADRIN study has gone beyond describing neonatal ADRs by evaluating the methodology that might be helpful when further assessing, understanding, and preventing them. The research has demonstrated a lack of appropriate ADR causality assessment methods that can reliably be used in the neonatal population. This is not the only area of research that is lacking in neonatal pharmacovigilance. A systematic review into ADRs in neonates should be carried out to determine the spread of neonatal ADRs seen worldwide and to identify other areas of research that may need expanding to maximise the safety of medicines in this population. Severity and avoidability assessment methods also need to be characterised.

It may take many years and significant work to bring pharmacovigilance practices in neonates in line with those of adult populations. Many aspects of neonatal care are advancing rapidly and a balanced assessment of benefits and harms of new and existing medicines is essential. Accordingly, research into the methodology of neonatal pharmacovigilance is of great importance.

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Appendix

Appendix 1 - Study protocol

ADRIN 1: Methodology

Adverse Drug Reactions in Neonates 1: What are the best ways to evaluate suspected adverse drug reactions in neonates?

Version 6. 04.10.16

Study Team

Chief Investigator:

Dr Mark Turner (Senior Lecturer in Neonatology / Honorary Consultant Neonatologist)

Co-investigators:

Eve Roberts (MPhil Student)

Dr Daniel Hawcutt (Senior Lecturer in Paediatric Clinical Pharmacology)

Clinical Queries

Clinical queries should be directed to Dr Mark Turner who will direct the query to the appropriate person.

Sponsor

The University of Liverpool is the research Sponsor for this Study. For further information regarding the sponsorship conditions, please contact:

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Funder

The project will be conducted by Eve Roberts, MPhil student, University of Liverpool.

No consumables are required for the running of this study and therefore no additional funding will be required.

STUDY SUMMARY

This protocol describes the ADRIN Methodology Study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

GLOSSARY OF ABBREVIATIONS

ADRIN Adverse Drug Reactions in Neonates

NICU Neonatal Intensive Care Unit

LWH Liverpool Women's Hospital

ADR Adverse Drug Reaction

MHRA Medicines and Healthcare products Regulatory Agency

SPSS Statistical Package for Social Sciences

TITLE

Adverse Drug Reactions in Neonates 1: What are the best ways to evaluate suspected adverse drug reactions in neonates?

DESIGN

Prospective observational cohort study

AIMS

a) To characterise causality, severity and avoidability tools used to evaluate possible ADRs to determine the use of these tools in the neonatal setting

b) To estimate the frequency of ADRs in neonates admitted to the NICU at Liverpool Women's Hospital over a 6-month period

c) To describe the ADRs, and identify risk factors for developing ADRs, in the neonatal population

d) To consider how reporting of ADRs in a neonatal setting may be improved by trialling a neonate-specific surveillance system and staff education and motivation interventions

OUTCOME MEASURES

•Recommendations about which causality, severity and avoidability assessments are appropriate for the evaluation of neonatal ADRs.

•Estimates of the frequency of suspected ADRs in neonates and further clinical details about suspected ADRs and the population affected. This aims to extend understanding of the nature of ADRs and potential risk factors for developing an ADR in the neonatal population

•Recommendations about surveillance for ADRs among neonates

POPULATION ELIGIBILITY

All neonates admitted to the neonatal unit at Liverpool Women's Hospital

DURATION

9 months

1. INTRODUCTION

1.1 BACKGROUND

The Liverpool Women's Hospital Neonatal Unit treats over 1000 neonates a year from all over the United Kingdom, from an approximate total of 90,000 neonates admitted to neonatal care each year in the UK (1) (2). Many of these neonates will be prescribed medicines, and yet most previous pharmacovigilance studies have omitted part or all of the inpatient neonatal population from their work. An adverse drug reaction is defined by the World Health Organisation as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man'(3). Recent studies into adverse drug reactions in children have indicated a considerable health risk for this population, with incidence rates ranging from 0.4% to 10.3% for paediatric hospital admissions related to ADRs and 0.6% to 16.8% for the proportion of children experiencing an ADR during their admission(4). Between 2000 and 2009 the highest number of ADR reports for children was in children under one year of age but to date there is limited research studying ADRs in neonates alone (5).

1.2 RATIONALE FOR CURRENT STUDY

ADRs are an important source of morbidity and resource use

A study set in two Merseyside hospitals found that 6.5% of admissions among adults related to an ADR, of which 80% were directly due to the ADR. These admissions accounted for 4% of the hospitals' bed capacity. When extrapolated to the whole NHS, the cost of ADRs was estimated to be £466m (2004; €706m, $847m) (6).

A similar study in a Merseyside children's hospital found that 2.9% of admissions were due to ADRs (7). Among children who spent more than 48 hours in hospital 18% experienced at least one ADR (8).

The team who conducted the paediatric study (Adverse Drug Reactions in Children, ADRIC) found that existing tools were difficult to use with children, particularly in-patients.

Neonates are often admitted for weeks or months after birth and are exposed to multiple medications. They are likely to suffer similar burdens of ADRs. This burden was described in the past and in the present (9) (10). However, patterns of care differ across time and place. The tools used to evaluate ADRs in neonates have not been characterised in detail and may not be appropriate.

There is a specific need to look for, and evaluate, suspected ADRs in neonates.

Neonates are subject to different adverse drug reaction profiles in comparison to older children and adults. The reasons behind this are multiple. The development of a child from conception to adulthood is dynamic, and changes in organ function and body composition affect pharmacodynamics and pharmacokinetics. There are further sources of ADRs to be considered in neonates including those drugs administered to the parents of the neonate pre-conception, in pregnancy, in labour and during breast feeding. As neonatal inpatients are often sick or premature neonates, they commonly receive multiple drugs and a linear correlation between the incidence of ADRs and exposure to four or more medications has been demonstrated (11). A study conducted in a neonatal intensive care unit reported that 29.6% of neonates received more than four medications and 7.6% received 10 or more (12). Further studies show that up to 90% of inpatient neonates in neonatal intensive care receive off-label or unlicensed medications which multiple studies suggest is a risk factor for developing an ADR (13) (14). There are also some medications which are uniquely harmful to neonates (15). Hence there is a need to study ADRs exclusively in this youngest group of patients.

When we studied ADRs in children we found that methods could not be transferred directly from adults. The methods currently available to evaluate suspected ADRs in neonates have been poorly characterised. Suspected ADRs need to be evaluated in several ways including causality, severity and avoidability. There are many ways to do each of these evaluations.

Causality: Naranjo was not suitable in children. In ADRIC a new tool was developed for children but this has not been assessed in neonates. A neonatal modification of Naranjo was developed recently in one centre but this has not been validated in another site.

Severity: Hartwig not suitable in neonates: severity may not be apparent and important changes may not affect care. A severity score is under development in Belgium and needs to be validated.

Avoidability: A paediatric avoidability score was developed in ADRIC but has not been validated in neonates.

Current surveillance methods are not adequate

Also concerning is the suspected rate of underreporting for ADRs in all populations which is estimated to be approximately 95% (16) (17). Premature neonates are considered to be at an increased risk of suffering from an unrecognised or unreported ADR due to diagnostic overshadowing commonly seen in prematurity.

In addition to the complex medical practice seen in neonatal care, there are few resources in place to encourage ADR reporting in this population. The MHRA advises the reporting of any suspected ADR in children, however a recent study reported that only 97 Yellow Cards were

completed for neonates in the 10-year period between 2001 and 2010(18). The current Yellow Card Scheme does not measure all outcomes needed to assess an ADR in a neonate. Reporting on factors which may have influenced the occurrence of an ADR in a neonate, such as gestational age at birth, are not routinely collected using the current Yellow Card Scheme and thus this area cannot be further studied unless provided voluntarily by the reporter. Some neonatal ADRs are being reported through the Yellow Card Scheme but to date no clinical warnings issued by the MHRA appear to have been influenced by those reports submitted in the UK (18).

Due to the highly demanding and emotive nature of neonatal care, ADR reporting is often overlooked in day to day practice. There is an aspect of educated guesswork in neonatal prescribing due to the lack of inclusion of children, infants and neonates in drug trials and so thorough pharmacovigilance in this population is vital.

2. STUDY OBJECTIVES

Primary objective:

a) To compare several causality, severity and avoidability tools used to evaluate possible ADRs to determine their use in the neonatal setting

Secondary objectives:

a) To make preliminary estimates of the frequency/incidence of ADRs in neonates admitted to the NICU at Liverpool Women's Hospital over a six-month period
b) To describe the ADRs, and identify risk factors for developing ADRs, in the neonatal population
c) To consider how reporting of ADRs in a neonatal setting may be improved including trialling a neonate-specific surveillance system and staff education and motivation interventions

3. STUDY DESIGN

Type of study:

A prospective observational cohort study carried out over nine months with detailed evaluation of cases of suspected ADRs

Type of subjects:

Neonates admitted to the LWH Neonatal care unit

Study setting:

Neonatal unit at the Liverpool Women's Hospital - all nurseries included

3.1 STUDY OUTCOME MEASURES

•Causality, severity and avoidability assessments of the collected ADR cases to enable further analysis to determine the use of such tools in a neonatal setting

•The frequency of suspected ADRs in neonates admitted to the NICU at the LWH and further clinical details about suspected ADRs and the population affected. This aims to demonstrate the nature of ADRs and potential risk factors for developing an ADR in the neonatal population

4. PARTICIPANT ENTRY

4.1 PARTICIPANT INCLUSION CRITERIA

Neonates admitted to the LWH Neonatal care unit

4.2 PARTICIPANT EXCLUSION CRITERIA

Neonates who are more than 28 days post their estimated date of delivery

4.3 WITHDRAWAL CRITERIA

N/A

4.4 DRUG INCLUSION CRITERIA

Continuous infusions, regular medications, stat/one-off and as-required drugs prescribed to the neonate, including parenteral nutrition

Continuous infusions, regular medications, stat/one-off and as-required drugs prescribed to the mother pre-conception, during pregnancy or labour or during breastfeeding/expressing breastmilk

4.5 DRUG EXCLUSION CRITERIA

•All blood products with the exception of immunoglobulins

•All enteral feeds

4.6 ADR INCLUSION CRITERIA

An ADR as defined by Allegaert et al as 'an unintended and harmful effect resulting from the use of medications intended for diagnostic or therapeutic reasons (irrespective of the

dose)'(19) experienced by any neonate and suspected to be caused by a drug which meets the inclusion criteria in this study. This definition was chosen to acknowledge the inclusion of off-label and unlicensed prescribing in this population.

4.7 ADR EXCLUSION CRITERIA

•Any ADR suspected to be caused by a drug excluded from the study

•Medication errors that are not associated with harm

5. STUDY METHODS

5.1 Overview of methods

All neonates will be reviewed using several methods:

1) Visit to the cot side by the researcher 4 – 5 times a week
2) Review of the clinical record including prescription charts and Pharmacy records
3) Questions to clinical staff by the researcher 4 – 5 times a week
4) Reporting cards for staff to use

If any of these methods yield a suspected ADR a detailed form about that episode will be completed using relevant information extracted from the clinical record.

No new data will be collected or recorded for the purposes of this study.

The data extract will be used to:

a) construct anonymised summaries of each episode – the summaries will be used to conduct reviews of the episode for causality, severity and avoidability

b) prepare aggregated, anonymised data to calculate frequencies of the events.

An aggregated, anonymised dataset for all neonates in the unit (with and without suspected ADRs) will be prepared in order to provide comparator data for frequencies.

5.2 DATA EXTRACTED FROM CLINICAL RECORD FOR ANALYSIS OF SUSPECTED ADRs

The following data will be recorded for any neonate suspected to be suffering from an ADR

- Study identifier (ADRIN ID number)
- Gender

- Gestational age at birth
- Birth weight
- Post-natal age
- Weight at time of event
- Multiple pregnancy status
- Date on day of event
- Medication history (including details of drug, dose, route, date started, date stopped, indication) within three days prior to the event
- Details of drug(s) suspected to be causing ADR – whether the drug was prescribed off-label or unlicensed
- Description of event (including signs and symptoms, change in observations, change in investigation results, drug changes/treatment required, details of re-challenge, patient history of this reaction, outcome of the reaction, date and timing of reaction, type A or B)
- Any significant event preceding reaction e.g. general anaesthetic
- Details of respiratory support (mechanical ventilation or non-invasive) in the three days prior to the event
- Ongoing medical or surgical conditions including congenital anomalies
- Past medical or surgical conditions
- Details of patient feeding within three days of the event
- Details of drugs taken by breastfeeding mother (including details of drug, dose, route, date started, date stopped, indication and whether the drug was prescribed off-label or unlicensed)
- APGAR scores at birth
- CRIB II score in first 24 hours of life
- Nature of birth including mode of delivery and complications in labour
- Details of drugs given to mother in labour (including details of drug, dose, route, date started, date stopped, indication)
- Details of drugs given to mother in pregnancy (including details of drug, dose, route, date started, date stopped, indication)
- Details of significant pregnancy history
- Details of significant maternal medical history
- Age, gravidity and parity of mother
- Details of report (including date, person raising ADR suspicion, person reporting ADR, data source, reminder to complete Yellow Card)

5.3 DATA SOURCES

The neonatal unit electronic notes database 'BadgerNet' will be the main source of data for this study. This has access to demographic details, admission and discharge details, medical notes, nursing notes, medication histories, laboratory results, imaging results, observation charts and other note and chart sections. Some data will also be collected from verbal conversations with staff caring for the patient.

In addition to the above methods, data collection forms will be available on the ward for use by any member of staff who wishes to complete a form for a neonate. There will also be a 'trigger tool' available on the ward- a concise form allowing a member of staff to alert the researcher to a suspected ADR that they think needs following up.

5.4 TIMING OF DATA COLLECTION:

During periods of data collection, the neonatal unit daily ward round will be attended by the researcher Monday - Friday. It is hoped that clinicians will inform the researcher of any possible ADR suspicions and this will be prompted by a single question on the daily review sheet. Any suspected ADR discussed on the ward round will be documented on the same day. Following the ward round a structured clinical review of the care notes on BadgerNet from the previous 24 hours will be undertaken for each patient to look for any further ADRs not discussed during the ward round. On a Monday, the previous 72 hours will be reviewed.

At the end of the study period, reports from BadgetNet for the data collection periods will be generated to provide denominator data for the study. The reports generated will include:

- The total number of neonates admitted to the unit
- The gestational ages at birth of all neonates admitted to the unit
- The birthweights of all neonates admitted to the unit
- The total number of drugs prescribed to each neonate during their admission
- The total number of neonates receiving each drug
- The total number of neonates diagnosed with predefined illnesses of interest

5.5 DATA HANDLING

Data will be recorded on a paper data collection form initially and then entered into a password locked study spreadsheet created for this study. The study spreadsheet will be stored on a password locked University computer based at LWH that is backed up regularly according to University Computer Services protocol.

Data will be recorded on the paper and spreadsheet using an ADRIN ID number (study number unique to the neonate) and the date of the event. A separate list of ADRIN ID numbers will be linked to neonate identifiers. That is, the data will be pseudoanonymised.

The study team will have responsibility for: data collection, recording and quality acting in accordance with the Data Protection Act.

Data will be retained for 21 years in light of the possibility that ADRs in neonates may have consequences in later life.

5.6 COMMUNICATING ADRS TO CLINICIANS

All ADRs that are deemed possible, probable or definite after the causality assessments have been carried out will be communicated to the lead consultant for the patient.

The CI, who is an experienced consultant neonatologist with expertise in reviewing ADRs, will be available at all times to review the clinical importance of data and findings

5.7 ADR REPORTING TO THE MHRA

After the causality assessments have been carried out, all ADRs that are deemed possible, probable or definite ADRs will be reported to the MHRA using the well-established Yellow Card Scheme. An electronic copy of the Yellow Card report will be sent to the lead consultant for the patient.

5.8 CAUSALITY ASSESSMENTS

This study will look into evaluating three causality tools for their use to assess ADRs in neonates. The three causality tools used will be:

1) The Liverpool Causality Assessment Tool (20)
2) New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units (21)
3) A tool used in a recent prospective cohort study of ADRs in neonates conducted in Spain (10)

Each ADR report will be assessed using all three causality tools by at least two independent assessors. All assessments with be done independently using anonymised event reports.

Re-challenge:

In this study, a re-challenge will be considered as the re-administration of a medicine before the neonate is finally discharged from the unit. A medication that is re-administered outside the neonatal unit at LWH will not be considered a re-challenge as this information would not

have been available at the time the first reaction occurred. This will aid the completion of the Liverpool Causality Assessment Tool.

If the outcome of the causality assessment is unanimous in all assessments the report will be filed and a Yellow Card report sent to the MHRA as outlined above.

If no consensus is reached the case will be reviewed by a senior investigator. They will not know the outcome of the previous assessments and a separate, causality assessment will be carried out. The outcome of this assessment will be considered as the final outcome and Yellow Card report will be sent to the MHRA if the ADR is deemed definite, probable or possible.

5.9 SEVERITY ASSESSMENTS

This study will look into evaluating two ADR severity assessment tools for their use to assess ADRs in neonates. The two severity tools used will be:

1) A new severity tool currently under development in Europe
2) A tool used in a recent prospective cohort study of ADRs in neonates conducted in Spain (10)

Each ADR report will be assessed using both severity tools by at least two independent assessors. All assessments with be done independently.

If the outcome of the severity assessment is the same in all assessments the case will be assigned a severity rating as per that tool.

If no consensus is reached the case will be reviewed by a senior investigator. They will not know the outcome of the previous assessments and a separate, severity assessment will be carried out. The outcome of this assessment will be considered as the final outcome and the case will be assigned a severity rating as per that tool.

5.10 AVOIDABILITY ASSESSMENTS

This study will look into evaluating two ADR avoidability assessment tools for their use to assess ADRs in neonates. The two severity tools used will be:

1) The Liverpool avoidability assessment tool (22)
2) The Hallas scale (23)

Each ADR report will be assessed using both avoidability tools by at least two independent assessors. All assessments with be done independently.

If the outcome of the avoidability assessment is the same in all assessments the case will be assigned an avoidability rating as per that tool.

If no consensus is reached the case will be reviewed by a senior investigator. They will not know the outcome of the previous assessments and a separate, avoidability assessment will be carried out. The outcome of this assessment will be considered as the final outcome and the case will be assigned an avoidability rating as per that tool.

5.11 STATISTICAL ANALYSIS

Following the completion of causality, severity and avoidability assessments, statistical analysis will be carried out in order to determine the use of these tools in the neonatal setting.

Appropriate statistical tests will be conducted using SPSS software and advice will be sought from a university statistician where required. 95% confidence intervals will be used where appropriate.

Percentage agreement for the separate causality, severity and avoidability tools will be estimated using a kappa statistic. Percentage disagreement will be calculated where assessment scores using the same tool for the same case by two or more investigators are discordant. A global kappa score to estimate agreement between three or more assessors will also be conducted. Pairwise kappa scores will then be compared with global kappa scores.

Statistical analysis as carried out in two recent papers will be used as a model to guide the analysis in this study (20, 21).

5.12 DISCONTINUATION RULES

Discontinuation rules are not anticipated to be required for this study

6. ADVERSE EVENTS

Although the study is about adverse events and ADRs, no adverse events are anticipated to arise because of the study. Any concerning behaviour noted throughout the duration of this study will be reported to Dr Mark Turner for further investigation.

Parents and visitors may become aware of the data collection. All unit staff will be briefed about the study so that they can explain to parents and visitors that the unit pay continuous

attention to the quality of care provided to the neonates and that this study is investigating how best to examine the impact of medicines on the neonates.

No neonates will receive any change of treatment because of this study.

7. STATISTICS AND DATA ANALYSIS

All data collected from this study will be entered into a password locked spreadsheet specifically designed for this study and carefully tabulated to allow further analysis

Data will be analysed using SPSS software. A p value of ≤ 0.05 will be considered significant for all data analysis.

Appropriate statistical tests will be used to analyse the data generated in this study and a university statistician consulted if further assistance required.

A comparison will be made between the number of Yellow Card reports generated in this study and the number of Yellow Card reports for neonates in a recent 10-year period as demonstrated in a recent review of all reports between 2001 and 2010(18).

7.1 SAMPLE SIZE

The primary goal of this study is to characterise tools used to evaluate suspected ADRs in neonates. The study needs to collect enough suspected ADRs to do this. Previous work has used between 50 and 100 cases of ADRs to do this.

A formal sample size calculation has not been calculated because:

1. Sample size calculations are not easy for comparative studies
2. The project is time-limited because it is an MPhil project.

On the basis of experience with ADRIC and previous surveillance for ADRs among neonates, the supervisors are confident that 6 – 9 months data collection is sufficient to gather enough suspected ADRs to characterise tools used to evaluate suspected ADRs and to address the secondary objectives.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the North West – Liverpool East Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval

letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent will not be obtained from participants in this study as only collection of routine clinical data is required and all data will be pseudoanonymised for analysis.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the Data Protection Act. Data will be recorded on a paper data collection form initially and then entered into a password locked study spreadsheet created for this study. The study spreadsheet will be stored on a password locked University computer based at LWH that is backed up regularly according to University Computer Services protocol.

Data will be recorded on the paper and spreadsheet using an ADRIN ID number (study number unique to the neonate) and the date of the event. A separate list of ADRIN ID numbers will be linked to neonate identifiers. That is, the data will be pseudoanonymised.

8.4 INDEMNITY

The University of Liverpool holds Indemnity and insurance cover with Marsh UK LTD, which apply to this study.

8.5 SPONSOR

The University of Liverpool will act as the Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

The project will be conducted by Eve Roberts, MPhil student, University of Liverpool.

No consumables are required for the running of this study and therefore no additional funding will be required.

8.7 AUDITS

The study may be subject to inspection and audit by the University of Liverpool under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be coordinated through Eve Roberts.

10. END OF STUDY

Latest date of participant recruitment to the study: 1st July 2017

The spreadsheet used for the storage and analysis of data recorded in this study will be closed one month after the recruitment of the last participant

Submission date: August 2017

11. ARCHIVING

Data will be retained for 21 years after the completion of this study in light of the possibility that ADRs in neonates may have consequences in later life.

Work completed on this study will be stored on M: Drive under the supervision of Dr Mark Turner. The password-protected computer used is located in a locked office at the Centre for Women's and Children's Health Research at the LWH. Access to this department is by activated staff identification badge only.

All data will be archived as per the guidance of the research and development department at the Liverpool Women's Hospital and further advice sought if required.

12. PUBLICATION POLICY

Results of this study will be:

- reported to Trust bodies
- presented at regional meetings
- submitted to MHRA
- submitted for publication by peer-reviewed journals.

13. REFERENCES

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14. APPENDICES

Date	Event
Wednesday 5th October 2016	Sponsorship application submitted to the University of Liverpool
Wednesday 19th October 2016	Review by JRO Non-Interventional Sponsorship Sub-Committee
Wednesday 25th October 2016	Latest date for outcome report from committee
October 2016	Finalise systematic review protocol and begin literature search Ethical approval application
November 2016	Continue systematic review and begin data collection
November 2016– April 2017	Data collection
May- August 2017	Final data collection, end of study, thesis write up and submission, corrections and Viva exam

Appendix 2 - ADR alert form

ADRIN Study ADR Alert form

Please complete this form if you believe a baby on the unit may have experienced an adverse drug reaction

Thank you in advance,

The Adverse Drug Reactions in Neonates team

Baby hospital number:	W
Date and time reaction suspected:	___:___am/pm ___/___/___
Brief detail of event (please include drug(s))	
Your name and role	

On completion please fold in half and leave in folder to be collected by research team

Appendix 3 - Causality tool evaluation form

Karch and Lasagna algorithm:

(Please rate the following aspects of the tool- strongly disagree, disagree, neither agree nor disagree, agree, strongly agree)

	SD	D	N	A	SA
The tool was easy to use					
The tool was appropriate to use for a neonatal ADR case					
The tool fairly assessed all causality aspects of the case					
I would use this tool if it were available in clinical practice					
Further comments about this tool:					

New Adverse Drug Reactions Algorithm for Infants in Neonatal Intensive Care Units:

(Please rate the following aspects of the tool- strongly disagree, disagree, neither agree nor disagree, agree, strongly agree)

	SD	D	N	A	SA
The tool was easy to use					
The tool was appropriate to use for a neonatal ADR case					
The tool fairly assessed all causality aspects of the case					
I would use this tool if it were available in clinical practice					
Further comments about this tool:					

Liverpool ADR Causality Assessment Tool:

(Please rate the following aspects of the tool- strongly disagree, disagree, neither agree nor disagree, agree, strongly agree)

	SD	D	N	A	SA
The tool was easy to use					
The tool was appropriate to use for a neonatal ADR case					
The tool fairly assessed all causality aspects of the case					
I would use this tool if it were available in clinical practice					
Further comments about this tool:					